CARBONYL COMPOUNDS: STILL CENTRAL TO ORGANIC SYNTHESIS

Aldrichimica ACTA

VOL. 41, NO. 4 • 2008

ALDRICH Chemistry

Formation of C–C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation: Vinylation, Allylation, and Enolate Addition

Amino Carbonyl Compounds in Organic Synthesis

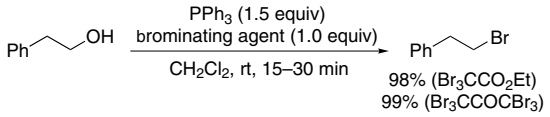
SIGMA-ALDRICH

New Products from Aldrich R&D

Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Reagents for the Bromination of Alcohols

There are various methods for the conversion of alcohols to bromides; however, commonly employed methods either use or generate toxic HBr gas. The use of hexabromoacetone ($Br_3CCOCBr_3$) and ethyl tribromoacetate (Br_3CCO_2Et) as less toxic, milder bromination reagents has recently been reported. Both reagents provide the desired alkyl bromide in excellent yield.



Tongkate, P. et al. *Tetrahedron Lett.* **2008**, *49*, 1146.

Ethyl tribromoacetate, 97%

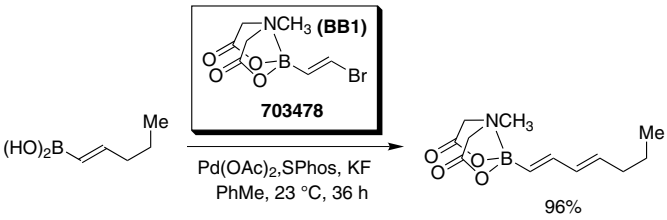
704679 — 1 g, 5 g
[599-99-5]
$C_4H_5Br_3O_2$
FW: 324.79

1,1,1,3,3,3-Hexabromoacetone, 97%

702404 — 5 g, 25 g
[23162-64-3]
C_3Br_6O
FW: 531.46

New Boronic Acid Surrogates for Iterative Cross-Coupling

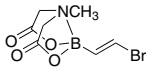
Professor Martin Burke and co-workers at the University of Illinois (Urbana-Champaign) have recently disclosed a technology employing boronic acid surrogates (termed "MIDA boronates") for use in iterative Suzuki cross-coupling reactions. The air-stable, chromatography-compatible, and easily deprotected boron building blocks permit difficult couplings through the attenuation of transmetallation via pyramidalization of the boron atom. The chemistry has been applied to the preparation of polyenyl MIDA boronates, for which the boronic acid counterpart is unstable. This subsequently led to the efficient synthesis of the left half of amphotericin B.



Lee, S. J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 466.

***trans*-2-Bromovinylboronic acid MIDA ester**

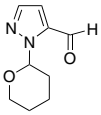
703478 — 500 mg, 1 g
$C_7H_9BBrNO_4$
FW: 261.87



New Aldehydes from Aldrich R&D

1-(2-Tetrahydropyranyl)-1*H*-pyrazole-5-carboxaldehyde

699365 — 1 g
[957483-88-4]
$C_9H_{12}N_2O_2$
FW: 180.20

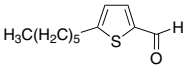


3-Methylpyridine-2-carboxaldehyde, 97%

699071 — 1 g
[55589-47-4]
C_7H_7NO
FW: 121.14

5-Hexylthiophene-2-carboxaldehyde, 97%

699187 — 1 g
[100943-46-2]
$C_{11}H_{16}OS$
FW: 196.31

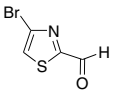


4-Oxazolecarboxaldehyde, 97%

697915 — 250 mg, 1 g
[118994-84-6]
$C_4H_3NO_2$
FW: 97.07

4-Bromothiazole-2-carboxaldehyde, 96%

699284 — 1 g
[167366-05-4]
C_4H_2BrNOS
FW: 192.03



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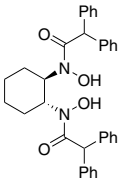
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Hisashi Yamamoto of The University of Chicago kindly suggested that we make bis(hydroxamic acid) based ligands, which, in combination with VO(O*i*-Pr)$_3$, generate highly active catalysts for the asymmetric epoxidation of allylic alcohols. Good-to-excellent yields and enantioselectivities of up to 97% ee have been reported.



Zhang, W. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

700592 (1*R*,2*R*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)-1,2-cyclohexanediamine, 97% 50 mg
(*R*)-CBHA-DPA

700576 (1*S*,2*S*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)-1,2-cyclohexanediamine, 97% 50 mg
(*S*)-CBHA-DPA

Naturally, we made these useful ligands. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

Pont Neuf, Paris (oil on canvas, 75.3 × 93.7 cm), was painted by the French Impressionist painter, Pierre Auguste Renoir (1841–1919), on a gloriously sunny and warm summer's day in 1872. While Renoir's paintings of women and children are better known, his landscapes resonate with a vigor and freshness new to the art scene at the time.

In this painting, Renoir uses a bright, light palette to emphasize an intense midday sun, but he deliberately suppresses incidental detail and clarity, displaying the basic tenets central to the development of Impressionism. Although Renoir presents us with an impressionistic view of the scene, the bridge and buildings in the background are accurate enough to be identifiable, then and now.

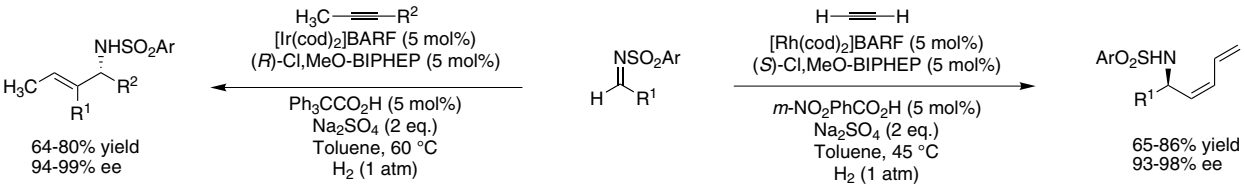
Renoir occupied an upper floor of a café on the left bank of the Seine to depict this famous view of the ninth bridge. Pont Neuf connects the Île de la Cité with the rest of Paris. Edmond Renoir, the artist's younger brother and novice journalist in 1872, later recounted in an interview that he helped his brother by periodically delaying a Parisian on the bridge long enough for the artist to record their appearance. Renoir captures Edmond, walking stick in hand, wearing a light-colored straw hat and slacks and a dark jacket in at least two locations. Can you find him?

This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

Metal Complexes and Ligands for Enantioselective Reductive Coupling

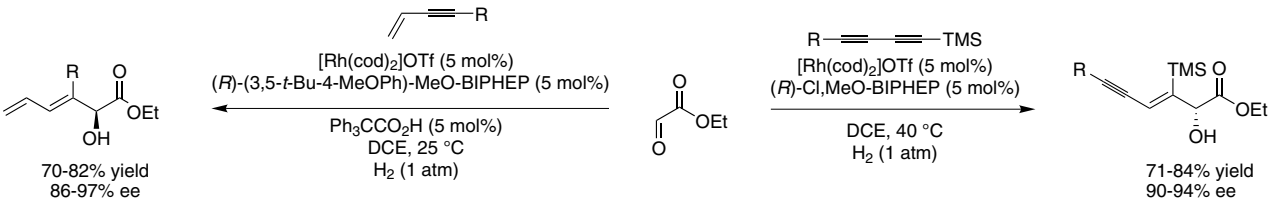
Asymmetric hydrogenation is one of the most utilized reactions to induce chirality in a molecule. It is currently widely used in industry. Krische and co-workers have developed a new type of transformation based on the enantioselective reductive C–C bond formation mediated by hydrogen. Utilizing a rhodium-, iridium-, or ruthenium-based complex with a variety of ligands, Krische and co-workers demonstrated the potency of this reaction for the reductive coupling of conjugated enones, dienes, imines, enynes, and carbonyls. Aldrich is offering a series of complexes and ligands for enantioselective reductive coupling.

Enantioselective Imine Vinylation

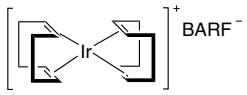


Ngai, M.-Y. et al. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Skucas, E. et al. *J. Am. Chem. Soc.* **2007**, *129*, 7242.

Enantioselective Reductive Coupling of Alkynes with Glyoxalates



Hong, Y.-T. et al. *Org. Lett.* **2007**, *9*, 3745. Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873.



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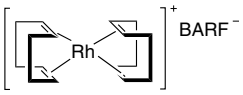

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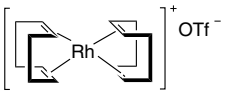

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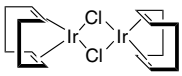

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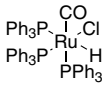

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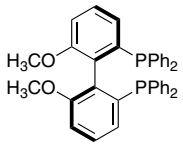
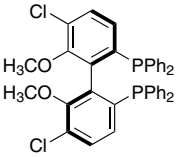
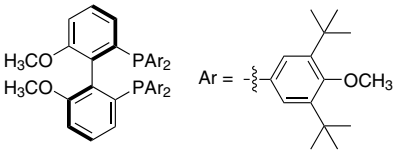


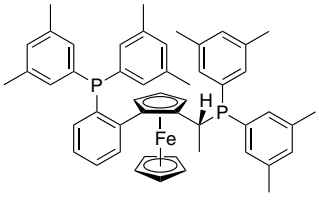
(R)-(+)-MeO-BIPHEP **29510**
(S)-(–)-MeO-BIPHEP **29511**



(R)-(–)-Cl,MeO-BIPHEP **76854**
(S)-(+)-Cl,MeO-BIPHEP **96738**



(R)-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29512**
(S)-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29513**

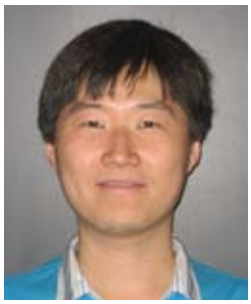


(R)-Xylyl-WALPHOS **65683**
(S)-Xylyl-WALPHOS **65684**

Formation of C–C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation: Vinylation, Allylation, and Enolate Addition

Mr. Ryan L. Patman

Dr. John F. Bower



Dr. In Su Kim

Prof. Michael J. Krische

*Ryan L. Patman, John F. Bower, In Su Kim, and Michael J. Krische**
Department of Chemistry and Biochemistry
University of Texas at Austin
1 University Station – A5300
Austin, TX 78712-1167, USA
Email: mkrische@mail.utexas.edu

Outline

1. Introduction

A fundamental challenge in organic chemistry resides in the development of efficient protocols for carbon–carbon-bond formation. The ideal C–C-bond forming processes should be applicable to both petrochemical and renewable feedstocks and should be aligned with the economic and aesthetic ideals of atom-economy,[1] step-economy,[2] and Green Chemistry.[3] Ultimately, chemical production should be sustainable, that is, it should not compromise human health, the environment, or the economy.

Hydrogen is vastly abundant, constituting roughly 90% of the atoms present in the Universe. Catalytic additions of elemental hydrogen, termed "hydrogenations," are of enormous socioeconomic importance. For example, the catalytic hydrogenation of atmospheric nitrogen to produce ammonia, the Haber–Bosch process,[4] is used to produce over 10^7 metric tons of ammonia annually. Nitrogenous fertilizer obtained from the Haber–Bosch process is estimated to sustain one-third of the Earth's population.[5] The asymmetric hydrogenation of C=X π bonds (X = O, NR) is estimated to account for over half of the chiral drugs manufactured industrially, not including those prepared via physical and enzymatic resolution.[6]

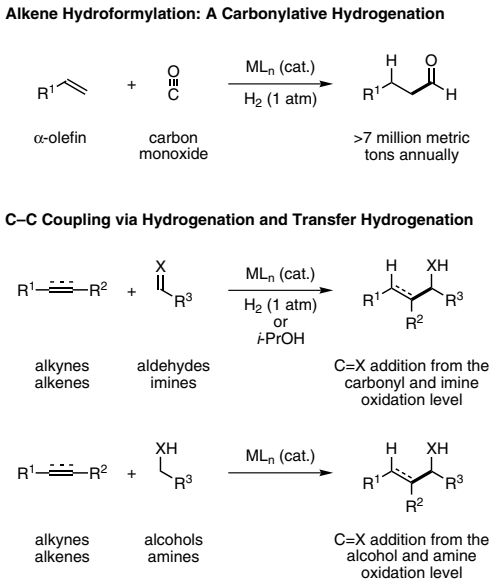
The Fischer–Tropsch reaction[7] and alkene hydroformylation[8] may be viewed as the prototypical C–C-bond forming hydrogenations. Hydroformylation combines basic feedstocks (α-olefins, carbon monoxide, and hydrogen) with perfect atom-economy, and accounts for the production of over 7 million metric tons of aldehyde annually, making it the largest-volume application of homogeneous metal catalysis.[9] Given the impact of hydroformylation, it is surprising that the field of "hydrogenative C–C-bond formation" lay fallow for over 70 years.[10,11]

As described herein, we have discovered that hydrogenation and transfer hydrogenation may be used to couple diverse π-unsaturated reactants to carbonyl compounds and imines.[12] Such hydrogenative C–C couplings define a departure from the use of preformed organometallic reagents in classical C=X (X = O, NR) addition reactions, in many cases enabling completely byproduct-free C=X addition processes. Furthermore, under transfer-hydrogenative coupling conditions, carbonyl addition can be achieved from the alcohol or aldehyde oxidation level,[12e,f] circumventing the redox manipulations typically required to adjust oxidation level (**Scheme 1**).

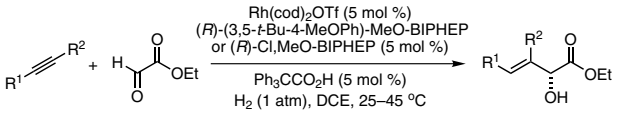
2. Vinylation of Carbonyl Compounds and Imines

Numerous methods exist for the preparation of allylic alcohols and allylic amines.[13,14] For example, metal-catalyzed allylic substitution employing oxygen and nitrogen nucleophiles is a powerful protocol for the synthesis of chiral nonracemic allylic alcohols and allylic amines.[15] Another approach, though less developed, involves catalytic enantioselective aldehyde vinylation.[16–19] Catalytic enantioselective vinyl transfer to imines had not been achieved prior to our work (vide infra).[20,21]

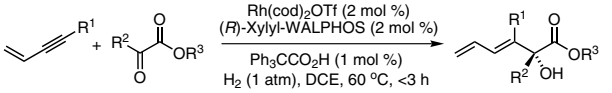
Limitations associated with the use of preformed vinyl metal reagents are potentially overcome through direct metal-catalyzed alkyne–carbonyl reductive couplings. The first catalytic process of this type, a rhodium-catalyzed reductive cyclization of acetylenic aldehydes mediated by silane, was reported in 1994 by Ojima et al.[22] In 1995, Crowe and Rachita disclosed related titanium-catalyzed cyclizations mediated by



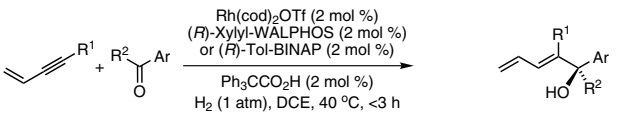
Scheme 1. Catalytic C–C Coupling via Hydrogenation and Transfer Hydrogenation.



R^1	R^2	Yield	ee
TBSOCH$_2$C≡C	TMS	72%	90%
PhC≡C	TMS	84%	91%
H$_2$C=CH	thien-2-yl	72%	92%
H$_2$C=CH	TESOCH$_2$CH$_2$	70%	90%



R^1	R^2	R^3	Yield	ee
BocNHCH$_2$	Me	Me	88%	90%
AcOCH$_2$	Me	Me	98%	90%
AcOCH$_2$	c-Pr	Me	85%	88%
n-Pent	Me	Et	96%	91%



R^1	R^2	Ar	Yield	ee
BocNHCH$_2$	c-Pr	pyridin-2-yl	89%	97%
AcOCH$_2$CH$_2$	H	1,5-Ph$_2$-pyrazol-3-yl	76%	92%
BocNHCH$_2$	Me	pyrazin-2-yl	92%	98%
Ph	H	5-Me-isoxazol-3-yl	73%	94%

Scheme 2. Direct, Byproduct-Free Hydrogenative Coupling of Conjugated Alkynes to Activated Carbonyl Compounds and Imines Employing Cationic Rhodium Catalysts. *(Ref. 27)*

silane.[23] Corresponding nickel-catalyzed cyclizations were first reported in 1997 by Montgomery and co-workers.[24a–c,e] Based on Montgomery's finding, nickel-catalyzed intermolecular alkyne–aldehyde reductive coupling was achieved by Jamison in 2000.[25] Improved nickel-based catalysts were developed later by Takai[26] and Montgomery.[24d] While reductive couplings of this type signal a departure from the use of preformed organometallic reagents, these methods employ terminal reductants such as hydrosilanes, hydrostannanes, organozinc reagents, organoboron reagents, or chromium(II) chloride and, hence, produce molar equivalents of metallic byproducts.

Under hydrogenation conditions, alkynes engage in completely byproduct-free reductive couplings to both carbonyl compounds and imines.[12d] First-generation catalytic systems based on rhodium promote the highly enantioselective coupling of conjugated alkynes to activated aldehydes and ketones in the form of vicinal dicarbonyl compounds.[27a–c] Heterocyclic aromatic aldehydes and ketones couple to conjugated alkynes under closely related conditions, providing access to heteroaryl-substituted carbinols.[27d] Notably, the diene- and enyne-containing products are not subject to over-reduction under the hydrogenative coupling conditions. Presumably, upon consumption of the electrophile (the limiting reagent) excess alkyne unproductively coordinates rhodium and so impedes the rate of further conventional hydrogenation (**Scheme 2**).[27]

The coupling of conjugated enynes or diynes to ethyl (*N*-sulfinyl)iminoacetates proceeds efficiently under the conditions of rhodium-catalyzed hydrogenation (**Scheme 3**).[28] Using appropriately substituted (*N*-sulfinyl)iminoacetates, one generates the corresponding β,γ-unsaturated α-amino acid esters as single diastereomers. A second hydrogenation of the unsaturated side chain of the coupling product provides access to β-substituted α-amino acids.

Gaseous acetylene couples to aldehydes and imines under hydrogenation conditions to furnish products of (*Z*)-butadienylation.[29] Using chirally modified rhodium catalysts, allylic alcohols and allylic amines are formed in highly optically enriched form (**Scheme 4**).[29,30] These byproduct-free couplings combine acetylene, an abundant feedstock,[31] with carbonyl compounds or imines to furnish chiral adducts in the absence of any preformed vinyl metal reagents.

Using second-generation catalysts based on iridium, highly enantioselective hydrogenative coupling of 1,2-dialkyl-substituted alkynes to *N*-arylsulfonyl imines is achieved (**Scheme 5**).[32] The trisubstituted allylic amine products are formed with complete levels of *E*:*Z* selectivity (≥95:5), and excellent regiocontrol is observed using nonsymmetric alkynes. This byproduct-free coupling provides trisubstituted allylic amines that are not accessible via metal-catalyzed asymmetric allylic alkylation.[15]

Finally, intramolecular coupling of alkynes to tethered aldehydes occurs readily in the rhodium-catalyzed hydrogenation. Using chirally modified catalysts, products of reductive carbocyclization are formed with uniformly high levels of optical enrichment.[33] Using an achiral rhodium catalyst, chiral racemic acetylenic aldehydes engage in highly *syn*-diastereoselective reductive cyclizations to furnish cyclic allylic alcohols (**Scheme 6**).

3. Allylation and Propargylation of Carbonyl Compounds

Carbonyl allylation is employed routinely in synthetic organic chemistry.[34] Asymmetric allylation has been achieved using chirally modified allyl metal reagents,[35] chiral Lewis acid catalysts, or chiral Lewis base catalysts.[36] These methods

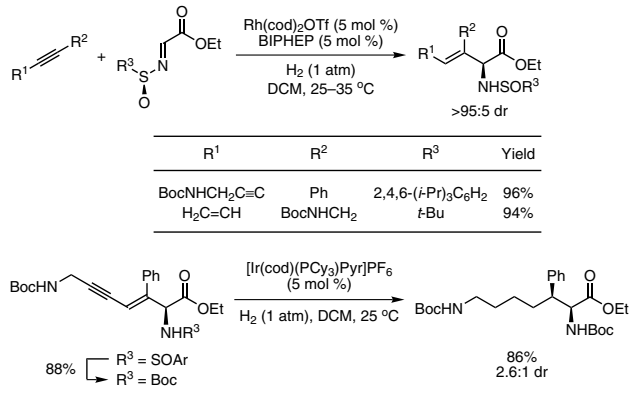
invariably employ preformed allyl metal reagents, such as allyl stannanes or trichlorosilanes, which generate stoichiometric quantities of metallic byproducts. Other methods for catalytic carbonyl allylation include the reduction of metallo-π-allyls derived from allylic alcohols and allylic carboxylates,[37] which require stoichiometric quantities of metal-based terminal reductants for catalytic turnover.[38]

We find that allyl metal species arising transiently in the course of allene hydrogenation may be captured by exogenous carbonyl electrophiles, thus enabling byproduct-free carbonyl allylation. For example, iridium-catalyzed hydrogenation of dimethylallene in the presence of activated aldehydes or ketones delivers products of reverse prenylation.[39a] Under the conditions of iridium-catalyzed transfer hydrogenation employing isopropanol as the terminal reductant, dimethylallene also couples to aldehydes.[39b] Finally, hydrogen embedded within an alcohol substrate can be redistributed among reactants to generate nucleophile–electrophile pairs, enabling byproduct-free carbonyl reverse prenylation *from the alcohol oxidation level* (**Scheme 7**).[39b]

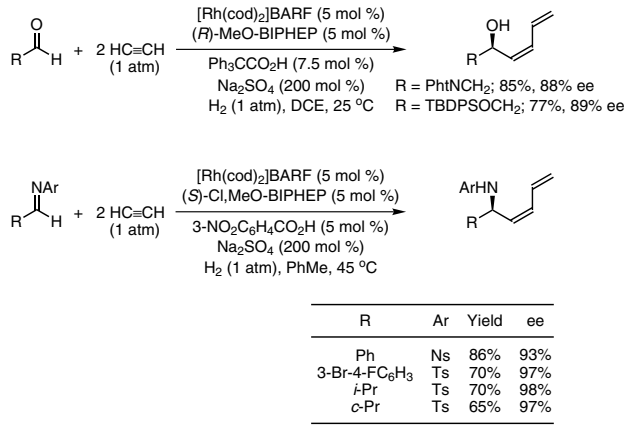
These results prompted efforts toward general catalytic protocols for alcohol–unsaturate transfer-hydrogenative coupling.[40] Under iridium-catalyzed transfer-hydrogenation conditions employing isopropanol as terminal reductant, 1,3-cyclohexadiene reductively couples to aldehydes. By exploiting alcohols as both hydrogen donors and aldehyde precursors, an identical set of carbonyl addition products is accessible from the alcohol oxidation level under nearly identical conditions (**Scheme 8**).[41] In the ruthenium-catalyzed transfer hydrogenation employing $RuHCl(CO)(PPh_3)_3$ as precatalyst, simple acyclic dienes (butadiene, isoprene, and 2,3-dimethylbutadiene) couple to diverse alcohols (**Scheme 9**).[42] Again, coupling is possible from the alcohol or aldehyde oxidation level. In the latter case, isopropanol or formic acid may be employed as terminal reductants.

Under the conditions of ruthenium-catalyzed transfer hydrogenation employing isopropanol as terminal reductant, conjugated enynes couple to aldehydes to furnish products of carbonyl propargylation (**Scheme 10**).[43–45] Under nearly identical conditions, the very same set of adducts is obtained directly from the corresponding benzylic, allylic, and aliphatic alcohols, which serve as both hydrogen donors and aldehyde precursors. Thus, carbonyl propargylation is achieved from the alcohol or the aldehyde oxidation level in the absence of preformed allenyl metal reagents. Stereocontrolled variants of these newly developed allene, diene, and enyne couplings are currently under investigation.

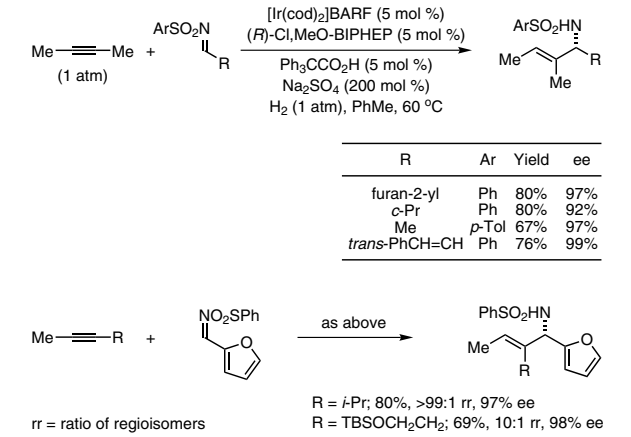
An especially powerful application of transfer hydrogenative C–C coupling involves iridium-catalyzed carbonyl allylation from the aldehyde or alcohol oxidation level employing allyl acetate as the allyl donor.[46a] Exposure of allyl acetate to benzylic alcohols in the presence of commercially available $[Ir(cod)Cl]_2$ and (*R*)-BINAP delivers products of *C*-allylation in good-to-excellent yields and with high levels of asymmetric induction. Allylation from the aldehyde oxidation level is achieved by employing isopropyl alcohol as the terminal reductant. In this case, (–)-TMBTP is used as the chiral phosphine ligand to generate identical allylation adducts with high degrees of enantioselectivity. Thus, asymmetric allylation is achieved from the alcohol or aldehyde oxidation level in the absense of preformed allyl metal reagents. More recently, this asymmetric allylation protocol has been extended to allylic alcohols and aliphatic alcohols (**Scheme 11**).[46b]



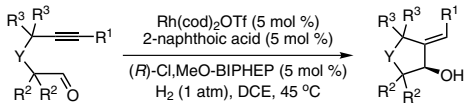
Scheme 3. Unnatural α-Amino Acids via C–C-Bond-Forming Hydrogenation. *(Ref. 28)*



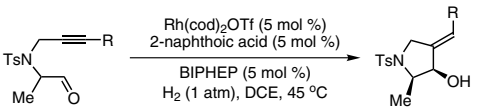
Scheme 4. Enantioselective Carbonyl and Imine (*Z*)-Butadienylation via Rhodium-Catalyzed Hydrogenative Coupling of Acetylene. *(Ref. 29,30)*



Scheme 5. Enantioselective Imine Vinylation via Iridium-Catalyzed Hydrogenative Coupling of Unconjugated Alkynes. *(Ref. 32b)*



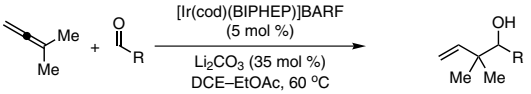
Y	R^1	R^2	R^3	Yield	ee
BnN	Me	H	=O	83%	99%
O	*n*-Hex	Me	H	86%	99%
TsN	Me	H	Me	63%	98%
TsN	H	Me	H	76%	96%



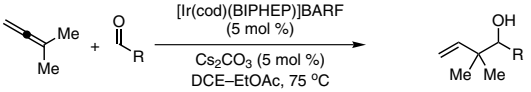
racemic

R = Ph; 95%, 8.3:1 dr
R = Me; 83%, >20:1 dr

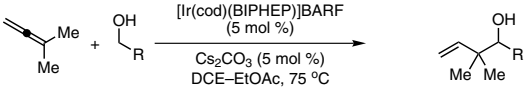
Scheme 6. Enantio- and Diastereoselective Carbocyclizations of Acetylenic Aldehydes via Rhodium-Catalyzed Asymmetric Hydrogenation. *(Ref. 33)*



R	Yield
$BnOCH_2$	80%
4-Br-3-$O_2NC_6H_3$	92%
Cbz	78%
6-Br-pyridin-2-yl	84%

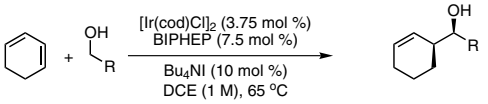


R	Yield
$PhtNCH_2$	57%
3-$MeOC_6H_4$	70%
Ph	81%
thien-2-yl	81%



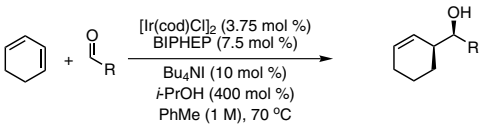
R	Yield
$PhtNCH_2$	84%
3-$MeOC_6H_4$	76%
Ph	90%
thien-2-yl	68%

Scheme 7. Catalytic Carbonyl Addition via Iridium-Catalyzed Hydrogenative Coupling of Dimethylallene. *(Ref. 39)*



R	Yield	1,4:1,5
3-$MeOC_6H_4$	95%	9:1
4-Br-3-$O_2NC_6H_3$	63%	15:1
1-Me-indol-2-yl	64%	8:1
thien-2-yl	85%	6:1

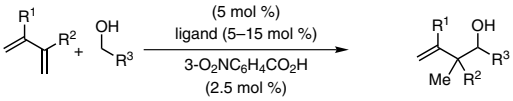
dr >95:5 in all cases. 1,4:1,5 is the ratio of the 1,4- to the 1,5-olefinic alcohol.



R	Yield	1,4:1,5
3-$MeOC_6H_4$	88%	17:1
4-Br-3-$O_2NC_6H_3$	73%	33:1
1-Me-indol-2-yl	77%	7:1
thien-2-yl	89%	10:1

dr >95:5 in all cases. 1,4:1,5 is the ratio of the 1,4- to the 1,5-olefinic alcohol.

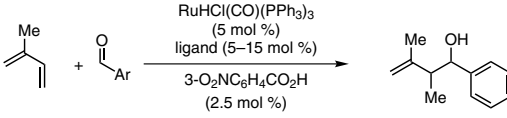
Scheme 8. Coupling of Dienes to Alcohols or Aldehydes via Iridium-Catalyzed Transfer Hydrogenation. *(Ref. 41)*



Ligand = P(4-$MeOC_6H_4$)$_3$ or *rac*-BINAP

R^1	R^2	R^3	Yield	dr
Me	H	*n*-Oct	65%	3:1
Me	H	*a*	75%	2:1
Me	Me	Ph	91%	—
H	H	thien-2-yl	87%	1.5:1

[a] R^3 = $Me_2C{=}CH(CH_2)_2C(Me){=}CH$.



Ligand = P(4-$MeOC_6H_4$)$_3$ or *rac*-BINAP

Terminal Reductant	X	Yield	dr
i-PrOH	NO_2	84%	2:1
i-PrOH	H	82%	2:1
i-PrOH	MeO	68%	1:1
HCO_2H	NO_2	89%	3:1
HCO_2H	H	64%	2:1
HCO_2H	MeO	68%	1:1

i-PrOH (400 mol %); HCO_2H (200 mol %).

Scheme 9. Coupling of Dienes to Alcohols or Aldehydes via Ruthenium-Catalyzed Transfer Hydrogenation. *(Ref. 42a)*

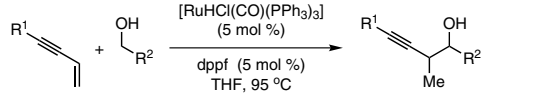
4. Hydrogenative Aldol and Mannich Additions

For well over a century, the aldol reaction has served as a core method in organic synthesis.[47] Intensive efforts have led to the realization of aldol addition protocols that enable excellent levels of diastereo- and enantiocontrol.[48] A particularly significant advance involves the refinement of methods for the direct asymmetric aldol additions of unmodified ketones employing metallic[49] or organic[50] catalysts. These byproduct-free processes herald a departure from the use of chiral auxiliaries and preformed enol(ate) derivatives. A significant limitation of these nascent technologies resides in the issue of regiocontrolled enolization. For example, direct catalytic asymmetric aldol additions of unsymmetrical ketones, such as 2-butanone, typically result in coupling at the less substituted enolizable position to furnish linear aldol adducts.[51]

The challenge of regiocontrolled enolization is overcome via enone reduction. Pioneering work by Stork demonstrates that dissolving metal reduction of enones enables regiospecific generation and capture of enolate isomers that cannot be prepared exclusively under standard conditions for base-mediated deprotonation.[52] Subsequently, catalytic reductive couplings of enones to aldehydes emerged.[53] To date, myriad metallic catalysts for "reductive aldol coupling" have been devised, including those based on rhodium,[54] cobalt,[55] iridium,[56] ruthenium,[57] palladium,[58] copper,[59,60] nickel,[61] and indium.[62,63] These protocols invariably employ metallic terminal reductants, such as stannanes, silanes, and organozinc reagents, which mandate the generation of stoichiometric byproducts. Inspired by the prospect of developing completely byproduct-free processes, catalytic reductive aldol additions employing elemental hydrogen as the terminal reductant were investigated.[64]

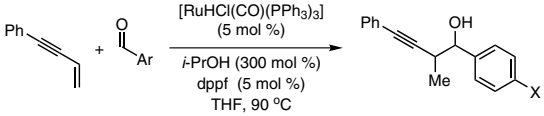
Our initial efforts centered on developing intramolecular reductive aldol couplings of tethered enone-aldehydes under hydrogenative conditions (**Scheme 12**).[64a] It was found that upon exposure to catalytic quantities of phosphine-modified cationic rhodium complexes under ambient pressures of hydrogen, a range of enone-aldehydes engage in highly diastereoselective cyclization to deliver five- and six-membered-ring products. In a similar fashion, enone-ketones cyclize to furnish *syn*-aldol adducts as single diastereomers.[64b] However, in these cases, the diminished electrophilicity of the ketone leads to substantial quantities of simple enone reduction product. Extension of this method to enone-diketone substrates provides a powerful desymmetrization strategy for the stereocontrolled generation of bicyclic frameworks bearing three contiguous stereocenters. The addition of aldehyde enolates to ketones, for which a single stoichiometric variant is known,[65] represents a highly challenging type of aldol addition. Under hydrogenative conditions, enal-ketones cyclize with a high degree of efficiency to provide products of aldehyde enolate-ketone addition, although competitive 1,4-reduction also is observed (**Scheme 13**).[64c]

Intermolecular hydrogenative aldol couplings also are possible. Under an atmosphere of hydrogen, cationic rhodium complexes catalyze the coupling of vinyl ketones to diverse aldehydes.[64a] Whereas the catalyst derived from $Rh(cod)_2OTf$ and triphenylphosphine provides aldol adducts as diastereomeric mixtures, high *syn*-diastereoselectivity is achieved using tri(2-furyl)phosphine as ligand.[64e,66] Under these modified conditions, a wide range of aldehydes couple to methyl or ethyl vinyl ketone with exceptional levels of *syn*-diastereoselectivity. Of note is the wide range of potentially "hydrogen-labile" functionality that is tolerated, thus enabling the use of substrates containing alkynes, alkenes, benzylic ethers, nitroarenes, and aryl bromides.



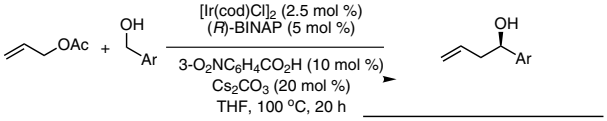
R^1	R^2	Yield	dr
$TBSOCH_2$	Ph	78%	1.5:1
Ph	*a*	63%	1.5:1
Ph	*n*-Pent	72%	2:1
Ph	1-Me-indol-2-yl	94%	1:1

[a] $R^2 = Me_2C{=}CH(CH_2)_2C(Me){=}CH$

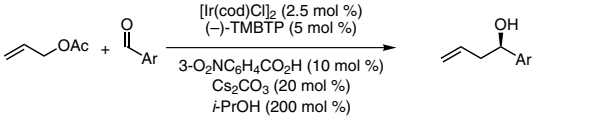


X	Yield	dr
NO_2	61%	1:1
H	74%	1:1
MeO	91%	1:1

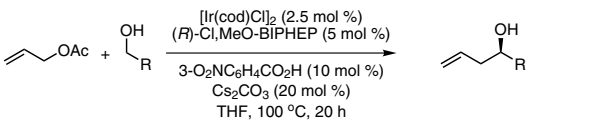
Scheme 10. Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level via Ruthenium-Catalyzed Transfer-Hydrogenative Coupling of 1,3-Enynes. *(Ref. 43)*



Ar	Yield	ee
$4\text{-}BrC_6H_4$	74%	93%
1-Me-indol-2-yl	55%	90%
$2\text{-}MeOC_6H_4$	80%	92%
$3,4\text{-}(OCH_2O)C_6H_3$	76%	91%

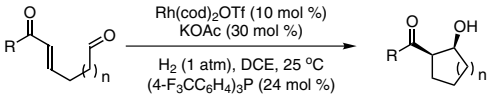


Ar	Yield	ee
$4\text{-}BrC_6H_4$	77%	97%
1-Me-indol-2-yl	82%	94%
$2\text{-}MeOC_6H_4$	86%	95%
$3,4\text{-}(OCH_2O)C_6H_3$	83%	94%



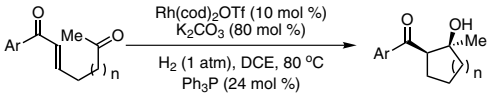
R	Yield	ee
$BnO(CH_2)_3$	78%	95%
$BnOCH_2C(Me_2)$	63%	93%
n-Oct	78%	95%
trans-PhCH=CH	72%	91%

Scheme 11. Enantioselective Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Iridium-Catalyzed Transfer-Hydrogenative Coupling of Allyl Acetate. *(Ref. 46b)*



R	n	Yield	syn:anti	1,4[a]
Ph	1	71%	24:1	1%
Ph	2	89%	10:1	0.1%
Me	2	65%	1:5	—
thien-2-yl	2	76%	19:1	2%

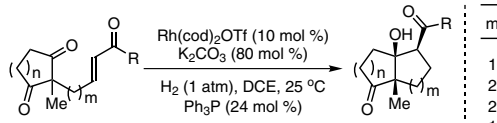
[a] Yield of the 1,4-reduction product.



Ar	n	Yield[a]	1,4[b]
2-Np	1	74%	18%
2-Np	2	78%	18%
thien-2-yl	1	66%	24%
thien-2-yl	2	78%	8%

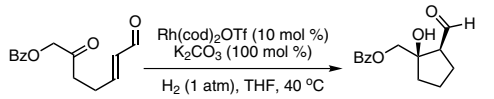
[a] In all cases, syn:anti >95:5. [b] Yield of the 1,4-reduction product.

Scheme 12. Reductive Aldol Cyclization via Catalytic Hydrogenation. *(Ref. 64a,b)*

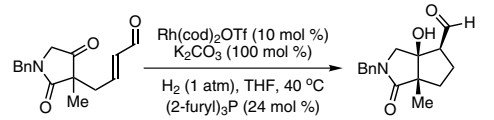


m	n	R	Yield[a]
1	1	Ph	84%
2	1	Ph	86%
2	2	Ph	65%[b]
1	2	Me	73%

[a] In all cases, syn:anti aldol >95:5. [b] 15% of the 1,4-redn prdt observed.



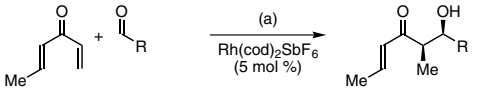
61%; syn:anti = 5:1
20% (1,4-redn prdt)



67%; syn:anti = 2:1
20% (1,4-redn prdt)

Scheme 13. Reductive Aldol Cyclization via Catalytic Hydrogenation. *(Ref. 64b,c)*

R1	R2	Yield	syn:anti
Me	4-O2NC6H4	91%	16:1
Et	4-O2NC6H4	90%	28:1
Me	BnOCH2	90%	17:1
Et	BnOCH2	88%	18:1
Me	PhC≡C	65%	8:1
Et	PhC≡C	70%	10:1
Me	PhtNCH2	95%	50:1
Et	PhtNCH2	97%	>99:1



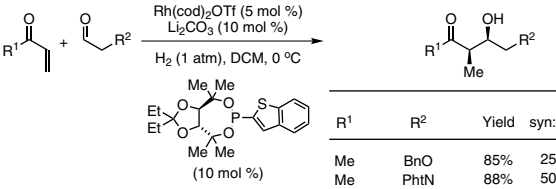
R	Yield	syn:anti
4-O2NC6H4	82%	13:1
BnOCH2	80%	9:1
6-Br-pyridin-2-yl	94%	11:1
PhtNCH2	85%	13:1

(a) Li_2CO_3 (10 mol %), H_2 (1 atm), DCM, 25 °C, (2-furyl)$_3$P (12 mol %)

R1	R2	Yield
Et	Bn	91%
Me	TBDPSOCH2	78%
Et	TBDPSOCH2	91%
Me	Bn	84%

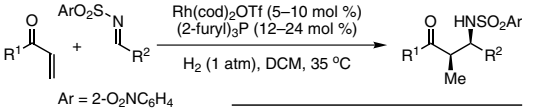
In all cases, dr ≥ 20:1.

Scheme 14. *syn*-Diastereoselective Hydrogen-Mediated Aldol Coupling Employing Cationic Rhodium Catalysts Ligated By Tri(2-furyl)phosphine. *(Ref. 64e–g)*



R1	R2	Yield	syn:anti	ee (syn)
Me	BnO	85%	25:1	91%
Me	PhtN	88%	50:1	96%
Et	1-Me-indol-3-yl	97%	25:1	90%
Et	Ph	76%	22:1	90%

eq 1 *(Ref. 64h)*



Ar = 2-$O_2NC_6H_4$

R1	R2	Yield	syn:anti
Et	4-O2NC6H4	80%	7:1
Me	3,4-Cl2C6H3	67%	9:1
Et	5-O2N-furan-2-yl	83%	4:1
Me	4-F3CC6H4	71%	6:1

eq 2 *(Ref. 67)*

Furthermore, functionalized enones also are tolerated, as demonstrated by the employment of crotyl vinyl ketone.[64f] Remarkably, the essentially neutral reaction conditions permit aldol coupling of configurationally sensitive *N*-Boc-α-amino aldehydes without racemization. Here, high levels of anti-Felkin–Anh control are achieved by taking advantage of hydrogen-bonded chelates, which arise in reaction media with low dielectric constants (**Scheme 14**).[64g]

The ability to access *syn*-aldol adducts relevant to polyketide synthesis inspired further efforts toward enantioselective variants. π-Acidic monodentate phosphine ligands are required to enforce high levels of diastereoselectivity and catalytic turnover. However, commercially available phosphines of this type (e.g., phosphoramidites and BINOL-derived phosphites) give rise to inactive rhodium complexes, suggesting a very narrow window in terms of ligand π acidity. Consequently, the design of an effective chiral monodentate phosphorus-based ligand was undertaken. The versatility of TADDOL-like phosphonites enabled the determination of key structure–selectivity trends, ultimately leading to the design of an effective ligand. Thus, by simply exposing methyl or ethyl vinyl ketone to aldehydes under an atmosphere of gaseous hydrogen in the presence of the rhodium phosphonite complex, aldol addition occurred with high levels of relative and absolute stereocontrol. This method generates optically enriched polyketide substructures and circumvents the stoichiometric generation of byproducts (**eq 1**).[64h]

Based on the preceding results, reductive Mannich couplings of vinyl ketones were explored.[67] Previously, reductive Mannich couplings had been accomplished using silane,[68] the Hantzsch ester,[69] or diethylzinc[70] as the terminal reductant. Under hydrogenative conditions employing a tri(2-furyl)phosphine-ligated rhodium catalyst, vinyl ketones couple to *N*-(*o*-nitrophenyl)sulfonyl aldimines to furnish the desired Mannich addition products with good levels of *syn*-diastereoselectivity (**eq 2**).[67] These preliminary studies suggest the feasibility of developing asymmetric variants of this transformation.

5. Future Directions

The stereoselective vinylation, allylation, and enolate addition of carbonyl compounds rank among the most broadly utilized methods in organic synthesis. Traditional protocols have relied upon the use of organometallic reagents, which are often basic, moisture sensitive, and give rise to stoichiometric quantities of metallic byproducts. Inspired by alkene hydroformylation and the parent Fischer–Tropsch reaction, hydrogenative variants of classical carbonyl addition processes are aimed at meeting the environmental, economic, and health and safety ideals set by Green Chemistry. For the hydrogenative protocols, carbonyl and imine addition occurs under essentially neutral conditions simply upon exposure of an unsaturate–electrophile pair to gaseous hydrogen in the presence of a metal catalyst. Accordingly, vinylation, allylation, and enolate addition are achieved without stoichiometric byproduct generation and with stereoselectivities often surpassing traditional methods. The discovery of related transfer-hydrogenative couplings not only evades the stoichiometric generation of metallic byproducts, but also the requirement for substrate oxidation level adjustment. The ability to perform carbonyl addition from either the aldehyde or alcohol oxidation level has broad implications for the field of organic synthesis. These nascent reactivity modes should serve as the basis for innumerable byproduct-free alcohol–unsaturate and amine–unsaturate coupling processes.

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Keywords: hydrogenation; transfer hydrogenation; allylic amines; aldol; allylation.

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Ryan L. Patman was born in 1982 in Elk City, Oklahoma. In 2006, he received a B.S. degree in chemistry from Oklahoma State University, where he conducted undergraduate research under the supervision of Professor Richard A. Bunce. He is currently a doctoral candidate in the research group of Professor Michael J. Krische at The University of Texas at Austin.

John F. Bower was born in 1980 in Chester, England. In 2003, he obtained an M.Sci. degree in chemistry from the University of Bristol, U.K., where he conducted research under the supervision of Professor Guy C. Lloyd-Jones. He continued with his doctoral studies at Bristol under the supervision of Professor Timothy Gallagher and, in 2007, received his Ph.D. degree. In May 2007, he joined the research group of Professor Michael J. Krische at The University of Texas at Austin as a postdoctoral research associate.

In Su Kim was born in 1975 in Gapyeong, Republic of Korea. In 2001, he received a B.S. degree from the College of Pharmacy, Sungkyunkwan University, Republic of Korea. He obtained an M.S. degree in 2003 and a Ph.D. degree in 2006, working under the guidance of Professor Young Hoon Jung. In September 2007, he joined the group of Professor Michael J. Krische at the University of Texas at Austin as a postdoctoral fellow of the Korea Research Foundation (KRF).

Michael J. Krische obtained a B.S. degree in chemistry from the University of California at Berkeley, where he performed research under the guidance of Professor Henry Rapoport as a President's Undergraduate Fellow. After one year of study abroad as a Fulbright Fellow, he initiated graduate research at Stanford University under the mentorship of Professor Barry Trost as a Veatch Graduate Fellow. Following receipt of his Ph.D. degree, he worked with Jean-Marie Lehn at the Université Louis Pasteur as an NIH Post-Doctoral Fellow. In the fall of 1999, he was appointed Assistant Professor at the University of Texas at Austin. He was promoted directly to Full Professor in 2004 and in 2007 he received the Robert A. Welch Chair in Science. Professor Krische's research program is focused on the development of C–C-bond-forming hydrogenations and transfer hydrogenations. Research from his laboratory demonstrates that hydrogenation and transfer hydrogenation may be used to couple diverse π-unsaturated reactants to carbonyl compounds, imines, and even alcohols offering a byproduct-free alternative to stoichiometrically preformed organometallics in a range of classical C=X (X = O, NR) addition processes. These studies represent the first systematic efforts to exploit hydrogenation in C–C couplings beyond hydroformylation, and define a departure from the use of preformed organometallic reagents in carbonyl and imine additions. His research accomplishments led to the receipt of numerous awards and honors: Tetrahedron Young Investigator Award (2009), Novartis Chemistry Lectureship (2008), Presidential Green Chemistry Award (2007), Dowpharma Prize (2007), ACS Elias J. Corey Award (2007), Solvias Ligand Prize (2006), Society of Synthetic Organic Chemistry, Japan Lectureship (2005), Johnson & Johnson Focused Giving Award (2005), Dreyfus Teacher Scholar Award (2003), Alfred P. Sloan Research Fellowship (2003), Cottrell Scholar Award (2002), Frasch Foundation Award in Chemistry (2002), Lilly Grantee Award (2002), National Science Foundation-CAREER Award (2000), Maître de Conference, Collège de France (1999), NIH Post-Doctoral Fellow (1997), Veatch Graduate Fellow (1995), Sigma Xi Grantee (1991), and Fulbright Fellow (1990).

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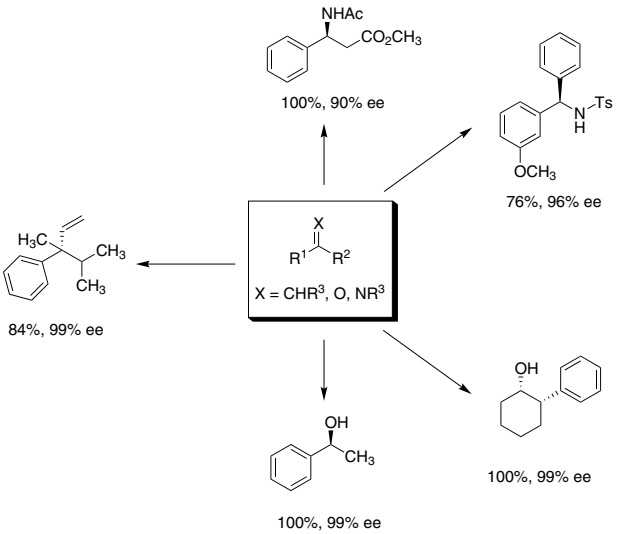
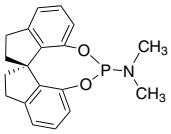
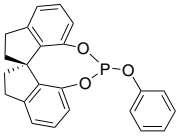
Asymmetric hydrogenation is playing a major role in the creation of chiral centers, and is widely used on a research and industrial production scale. Some of the most common ligands for asymmetric hydrogenation are C_2-symmetrical phosphines, of which the most notable ones are BINAP, DIPAMP, or TADDOL. Zhou and co-workers have developed a new type of C_2-symmetrical ligand with 1,1′-spirobi-indane as backbone, and which offers higher enantiocontrol. It has shown excellent reactivity and selectivity in a variety of asymmetric hydrogenations. Aldrich is pleased to offer a library of these new ligands.





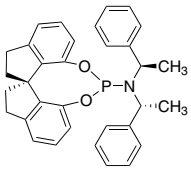
(*R*)-SIPHOS
700797

(*S*)-SIPHOS
700789



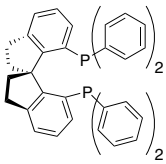
(*R*)-ShiP
700800

(*S*)-ShiP
700819



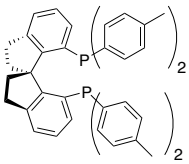
(*R*)-SIPHOS-PE
700770

(*S*)-SIPHOS-PE
700762



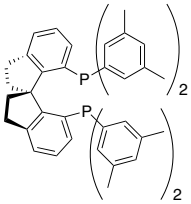
(*R*)-SDP
700754

(*S*)-SDP
700746



(*R*)-Tol-SDP
700827

(*S*)-Tol-SDP
700835



(*R*)-Xyl-SDP
700843

(*S*)-Xyl-SDP
700851

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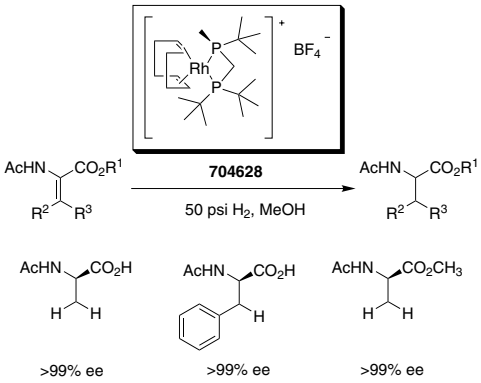
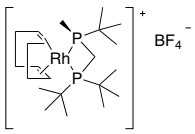
Asymmetric Hydrogenation of α-Acetamido Dehydroamino Acids

The importance of asymmetric hydrogenation is highlighted by the everyday use of this transformation in industry. The most common chiral ligands used for these reactions have C_2-symmetry. Hoge et al. have developed a new chiral ligand with a C_1-symmetry and used it with rhodium for the asymmetric hydrogenation of α-acetamido dehydroamino acids. Excellent selectivity was observed in the hydrogenation of a variety of α-acetamido dehydroamino acids.





704628

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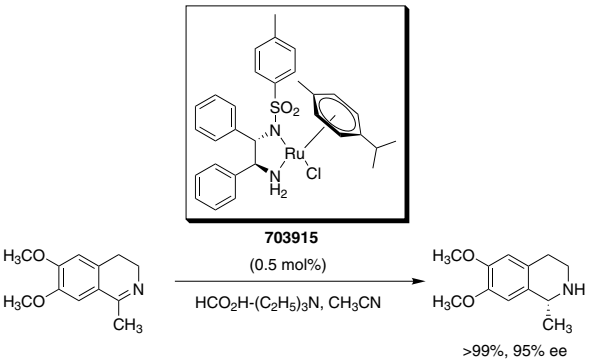
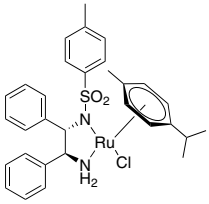
Hoge, G. et al. *J. Am. Chem. Soc.* **2004**, *126*, 5966.

Asymmetric Transfer Hydrogenation of Imines

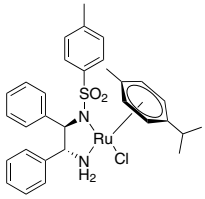
The use of transfer hydrogenation to reduce alkenes, carboxyl groups, or imines is becoming an increasingly attractive procedure. Uematsu et al. reported the asymmetric transfer hydrogenation of a variety of imines using a chiral diamine ligand complexed with ruthenium. A low loading of the catalyst is sufficient, and good yields and excellent stereoselectivities are observed.



Uematsu, N. et al. *J. Am. Chem. Soc.* **1996**, *118,* 4916.



RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN]
703915



RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN]
703907

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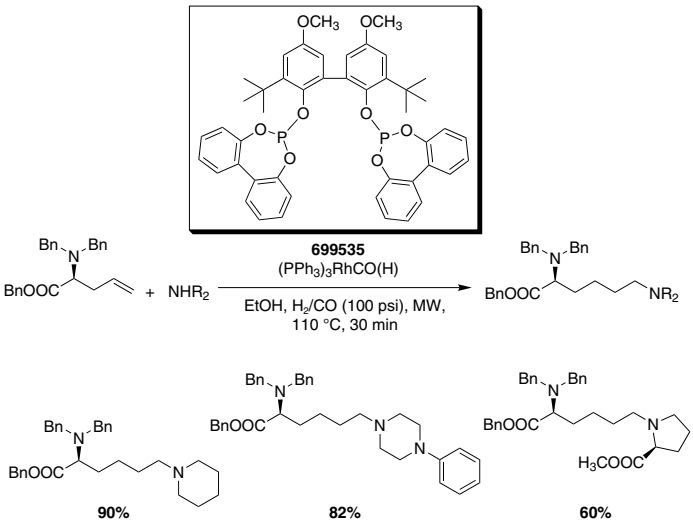
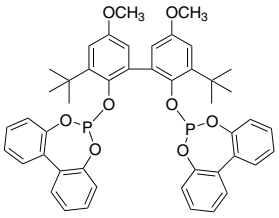
Hydroaminomethylation of Alkenes

The direct hydroamination of terminal alkenes is an interesting reaction due to its atom economy. However, only a few groups have taken advantage of this reaction. Petricci et al. reported the hydroamination of alkenes using BiPhePhos with a rhodium complex under microwave irradiation. Using this technique resulted in high conversion and selectivity, and reduced the reaction time.



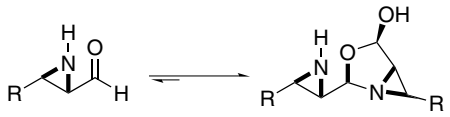


BiPhePhos
699535

Petricci, E. et al. *Tetrahedron Lett.* **2008**, *48*, 8501.

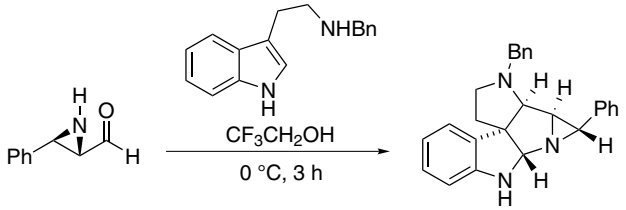
Discover Unprotected Amino Aldehydes from Professor Yudin

Professor Andrei Yudin and co-workers have recently described the preparation of bench-stable, unprotected α-amino aldehydes.[1] These kinetically amphoteric molecules exist as dimers, and due to the strain of the aziridine ring, resist inter- and intramolecular iminium ion formation. Furthermore, the two functionalities remain orthogonal to each other throughout their transformations, allowing for the reaction of the aldehyde without the requirement of an additional protecting group.



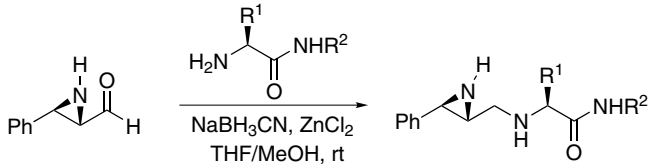
Whereas the reductive amination of protected amino aldehydes has significant limitations due to epimerization or overalkylation, these Yudin amino aldehyde dimers do not suffer from either limitation, due to a negligible concentration of free aldehyde during the reaction. This allows the researcher facile access to a method for the creation of complex polycyclic skeletons[2] or peptidomimetic conjugates[3] with a high degree of stereocontrol. Nucleophilic additions,[4] Wittig and related olefination reactions can be carried out with high selectivities and yields. Sigma-Aldrich is pleased to offer these useful Yudin amino aldehydes for your research.

Cascade Polycyclizations



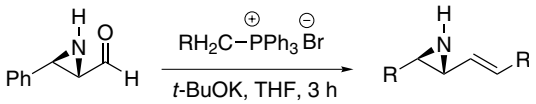
97%

Synthesis of Peptidomimetic Conjugates Without Protecting Groups



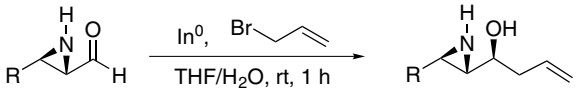
75 - 86%

Unprotected Vinyl Aziridines via Olefination

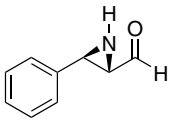


70-95%

Unprotected Vicinal 1,2-Amino Alcohols via Allylation with Indium Reagents



81-96%
>99% diastereoselectivity



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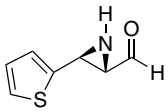

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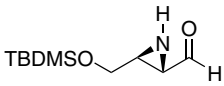

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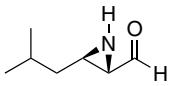

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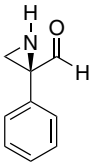

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Amino Carbonyl Compounds in Organic Synthesis


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Outline

1. Introduction

Amino aldehydes and amino ketones, $R^1C(=O)(CH_2)_nCHR^2NHR^3$, are versatile building blocks that are indispensable in the synthesis of natural products and pharmaceuticals. Their utility stems from the broad scope of synthetic transformations available to both the amino and carbonyl functional groups. However, the utility of amino aldehydes and ketones is not without shortcomings, as nitrogen- or carbon-protecting groups are usually needed in order to prevent undesired inter- and intramolecular self-condensation reactions. While serving to prevent these undesired processes, nitrogen protection can also have a detrimental effect on subsequent transformations of the carbonyl group. This review focuses on recent advances in the field of amino carbonyl chemistry.

1.1. Involvement of Amino Carbonyl Compounds in Biosynthesis

The versatility of amino carbonyl compounds is amply represented in complex alkaloid biosynthesis. Exquisitely tuned enzymatic cascades have evolved to handle the chemically incompatible carbonyl and amine functionalities. The biosynthesis of retronecine[1] is an instructive case: at least two points in its biosynthetic cascade incorporate transiently formed intermediates with a 1,5-aldehyde–amine relationship. Another well-known case is that of morphine (**1**), an archetypal opioid exhibiting potent analgesic effects on the central nervous system (**Figure 1, Part A**). The biosynthetic pathway to morphine involves stable amino carbonyl compounds such as neopinone and codeinone. The semi-synthetic opioid noroxymorphone (**2**), which contains a demethylated nitrogen, is also stable and has been used as an intermediate in the synthesis of other opioid receptor agonists.[2] Amino sugars belong to yet another class of naturally occurring amino carbonyl compounds. These molecules are important constituents of glycoproteins and glycolipids and are implicated in a vast range of cellular recognition events. Among the most commonly encountered monoaminosaccharides are glucosamine, *N*-acetylglucosamine, galactosamine, and *N*-acetylgalactosamine (**Figure 1, Part B**). Some of the most widely used antibiotics including vancomycin, erythromycin, and streptomycin contain amino sugar substituents.

1.2. Physical Properties of Amino Carbonyl Compounds

The first documented attempt at a chemical synthesis of an unprotected α-amino aldehyde was made by Fischer and Leuchs in 1903 when they reported the synthesis of *d*-glucosamine.[3] Although the aldehyde functionality in this molecule is masked as a hemiacetal, the equilibrium with an open-chain form predisposes glucosamine to self-condensation reactions. Therefore, this molecule is only stable in the salt form. Fischer later attempted to synthesize glycinal, which could not be isolated and was characterized through degradation studies. Almost a century later, Myers and co-workers demonstrated that α-amino aldehydes are autoprotective at acidic pH, whereby the amine group is present as the strongly electron-withdrawing ammonium ion and the aldehyde group exists as its tetrahedral solvent adduct.[4]

In chemical synthesis, the innate incompatibility between amine and aldehyde functionalities has been circumvented through the use of protecting groups. Protected α-amino aldehydes are relatively unstable, both chemically and configurationally, particularly in solution or in the course of chromatographic purification. The enantiomeric integrity of α-amino aldehydes largely depends on their structure, especially in terms of inter- or intramolecular stabilization.[5] Ito et al. undertook a comprehensive study of the loss of enantiomeric purity of N-protected α-amino aldehydes during chromatography on silica gel.[5] The

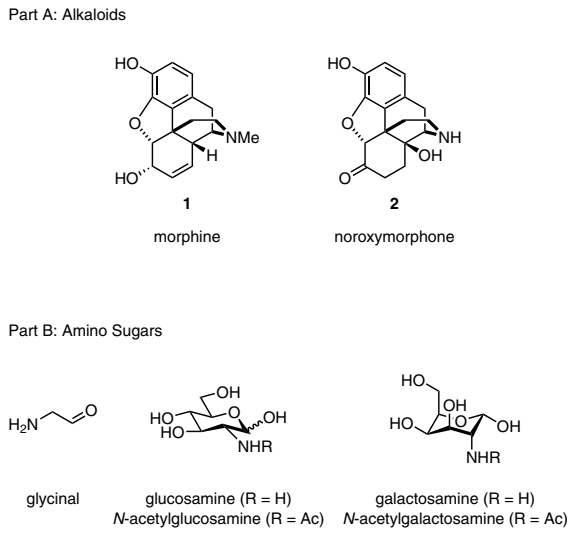
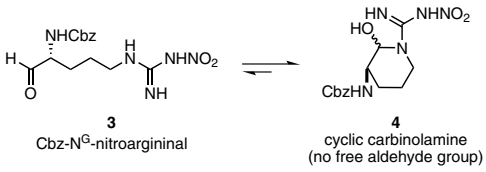
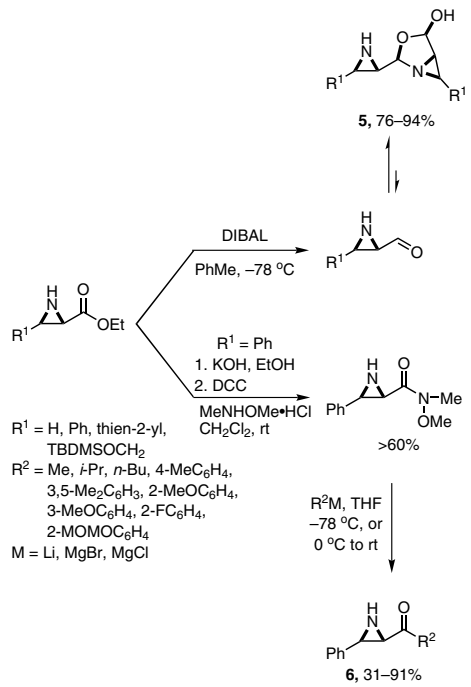


Figure 1. Alkaloids (Part A) and Amino Sugars (Part B) That Are Available Biosynthetically from Amino Carbonyl Compounds. *(Ref. 2,3)*



eq 1 *(Ref. 5)*



Scheme 1. Preparation of Unprotected α-Amino Carbonyl Compounds from Aziridine-2-carboxylates. *(Ref. 10)*

configurational stability of α-amino aldehydes on silica gel decreases in the following order: Cbz-*S*-Bzl-L-cysteinal >> Cbz-phenylalaninal > Cbz-leucinal >> Cbz-N^G-nitroargininal. The capacity of **3** to cyclize into hemiaminal **4** significantly impedes the racemization process (**eq 1**).[5] It is by this cyclization that the configurational stability of *Z*-*N*-nitro-L-argininal is maintained. The enantiomeric integrity of α-amino aldehydes can also be preserved by masking the aldehyde in either imidazolidine or acetal form.[6] These valuable intermediates can be purified by chromatography. In some cases, low temperatures may suffice for brief storage of unstabilized N-protected amino aldehydes.[7]

C-Protected amino aldehydes in which the amino group is free and the aldehyde is masked have been much less explored.[8] The carbonyl group of amino aldehydes can be protected as an acetal or an amino nitrile. C-Protected amino aldehydes have served as strategic precursors in the synthesis of saframycin A and its analogues.[9]

2. Preparation of Amino Aldehydes and Amino Ketones

The development of stable, unprotected amino carbonyl compounds has been a challenge in organic synthesis, not only from the standpoint of atom economy, but also from the standpoint of avoiding racemization. A few recent examples of stable, unprotected amino carbonyl compounds have been disclosed. Our group has described the preparation of unprotected α-amino aldehydes and ketones such as **5** and **6** from aziridine-2-carboxylate esters.[10] The α-amino aldehydes exist as dimers, whereas the corresponding ketones are monomeric compounds. Their stability is attributed to the increase in ring strain that would have accompanied self-condensation via iminium ion formation. For a similar reason, the α center of aziridine carbonyl compounds is not epimerizable (**Scheme 1**).

2.1. α-Amino Aldehydes and Ketones

Garner's aldehyde,[11] Reetz's *N,N*-dibenzyl and *N*-benzyl aldehydes,[12] as well as N-monoprotected and N,N-diprotected amino aldehydes are among the most widely utilized amino aldehyde derivatives.[13] Their general synthesis is outlined in **Scheme 2**. The most commonly used method is the reduction of carboxylic acid esters by diisobutylaluminum hydride (DIBAL), but in many cases over-reduction to the respective alcohol has been observed. In a few cases, the reduction with DIBAL can lead to erosion of enantiomeric purity by as much as 15%. However, DIBAL reduction of *N*-Boc amino acids, commonly used in peptide chemistry, gives the corresponding aldehydes without appreciable racemization. The alcohol is generally obtained through initial reduction of the corresponding α-amino acid or ester, which is then followed by oxidation. The final step can be carried out using a wide range of methods including Swern, Dess–Martin, or Parikh–Doering oxidations.

Weinreb amides are very useful in the preparation of α-amino aldehydes and ketones due to the fact that over-reduction and racemization are not observed (**Scheme 3**). These intermediates can be reduced to the aldehydes[14] in the presence of $LiAlH_4$, $LiAl(t\text{-}BuO)_3H$, or lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (LTEPA). A wide range of N-protecting groups are stable under these conditions. A kilogram-scale preparation of an α-amino aldehyde was reported by Schwindt et al. using sodium bis(2-methoxyethoxy)aluminum hydride (Vitride® or Red-Al®).[14d] This is an attractive alternative to other methods of reduction and a useful way to synthesize ketones,[15] including pentafluoroethyl ketones,[15a] and β-ketophosphonates.[15b]

The catalytic enantioselective α amination of aldehydes is a recent approach to the synthesis of α-amino aldehydes.[16] The research groups of List[17] and Jørgensen[18] independently developed the enantioselective synthesis of α-amino aldehydes by using the L-proline-catalyzed α amination of aldehydes (**eq 2**). This direct C–N-bond-forming reaction affords high levels of enantioselectivity in the formation of a stereogenic α-carbon center. Thus, propanal (**7**, R^1 = Me) reacts with diethyl azodicarboxylate (**8**, R^2 = Et) in the presence of L-proline as catalyst to give the corresponding amination product, **9**, in 93% yield and 92% ee. The reaction proceeds with low catalyst loadings and can be performed on a gram scale with high yields and enantioselectivities. The main drawback to this approach is that the products formed by the direct α amination of aldehydes display a gradual decrease in enantiomeric purity because of the acidity of the α proton. In addition, cleavage of the N–N bond requires harsh conditions.

As previously mentioned, enantiopure α-amino ketones have been prepared by reaction of organolithium and Grignard reagents with suitably N-protected α-amino acid derivatives. Recently, the catalytic asymmetric amination of ketones has become prominent in the synthesis of α-amino ketones. Johnson and co-workers[19] reported an enantioselective addition of acylsilanes to nitrone electrophiles in the presence of metallophosphite ligands. The key requirement for this reaction is an energetically accessible pathway for silyl transfer (**eq 3**).

Hashimoto and co-workers have reported a catalytic, enantioselective amination of silyl enol ethers with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane in the presence of dirhodium(II) catalyst **10**.[20] The chiral amino ketone obtained by this method has been employed in the formal synthesis of (–)-metazocine, a benzomorphan analgesic (**Scheme 4**). Osmium-catalyzed ketamination of alkenes was developed by Muñiz into an efficient route to α-amino ketones.[20b]

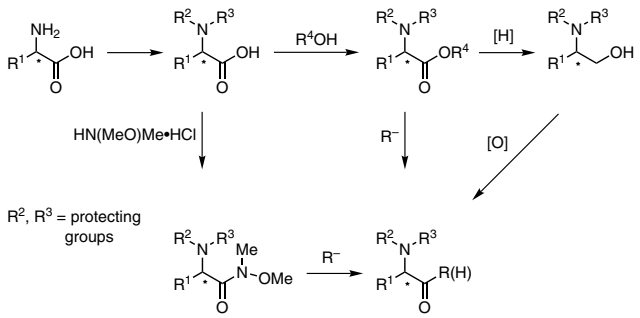
Mattson and Scheidt[21] have reported the synthesis of amino ketone **13** by reaction of acylsilanes **11** with imines **12** in the presence of carbene catalysts, which are generated in situ from readily available thiazolium salts. Furthermore, the authors showed that this method tolerates a wide range of acylsilanes and imines (**eq 4**).

Davis and co-workers[22] have described an effective way to synthesize C- and N-protected amino ketones from sulfinimines **14** with the aid of lithio-1,3-dithianes. α-Amino-1,3-dithioketals **16** and *N*-sulfinyl-α-amino ketones **17** were obtained after selective removal of the sulfinyl and thioketal groups, respectively (**Scheme 5**). This approach was employed in the asymmetric synthesis of (2*S*,3*R*)-(–)-3-hydroxy-3-methylproline (**18**), a polyoxypeptin amino acid.

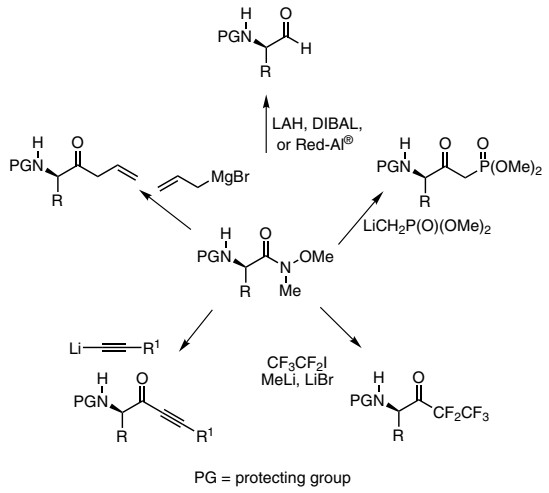
The organocatalytic asymmetric Mannich reaction is an efficient method for the synthesis of amino ketones. Recently, Barbas and co-workers[23] reported the synthesis of chiral 1,2- and 1,4-diamines **19** and **20** from azido ketones and phthalimido ketones, respectively, in the presence of an L-proline-derived tetrazole catalyst. Enantioselectivities of up to 99% have been achieved. The regioselectivity was found to depend on the nitrogen protecting group (**Scheme 6**).

2.2. β-Amino Aldehydes and Ketones

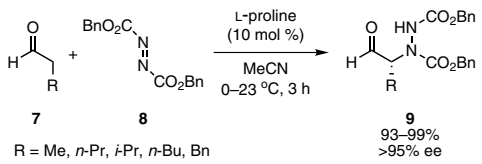
β-Amino acids are less abundant in nature than the corresponding α-amino acids. However, they do play important biological roles and have considerable potential for the stabilization of peptide-based drugs against proteolytic degradation. In general, β-amino aldehydes are not stable due to polymerization, self-condensation,



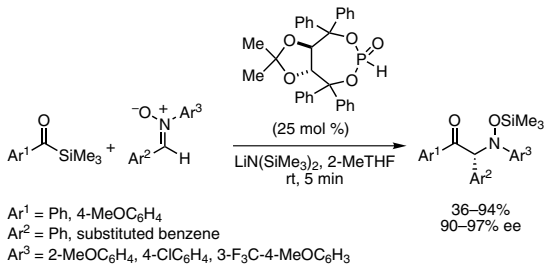
Scheme 2. General Synthesis of α-Amino Aldehydes and Ketones.



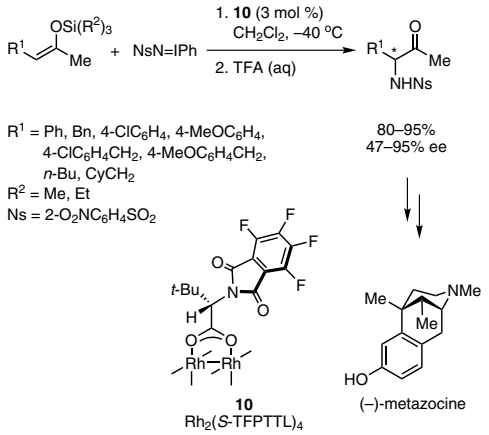
Scheme 3. α-Amino Carbonyl Compounds from Weinreb Amides. *(Ref. 14,15)*



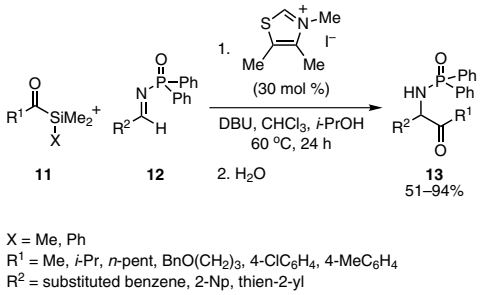
eq 2 *(Ref. 17)*



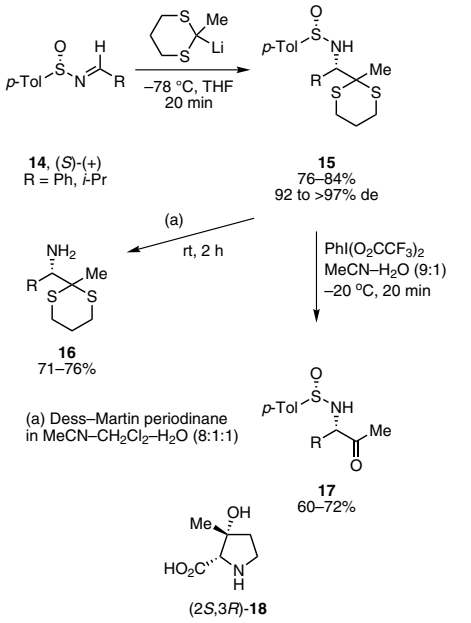
eq 3 *(Ref. 19)*



Scheme 4. Chiral α-Amino Ketones by the Enantioselective Amination of Silyl Enol Ethers. *(Ref. 20)*



eq 4 *(Ref. 21)*



Scheme 5. C- and N-Protected α-Amino Ketones from Sulfinimines. *(Ref. 22)*

or elimination of the β-amino group.[24] While one can obtain the β-amino carbonyl compounds from the corresponding α-amino acids, the most common approach toward their synthesis is to utilize Mannich-type reactions (**Scheme 7**).[25] This approach suffers from difficulties in controlling both the regio- and stereoselectivity. Some improvements have been made through the employment of Brønsted acids,[26] cinchona alkaloids,[27] phase-transfer catalysts,[28] metal catalysts,[29] and modified organocatalysts.[30]

List reported the proline-catalyzed asymmetric and diastereoselective Mannich reaction in 2000.[31] Recently, Barbas's[32] and Maruoka's[33] groups independently developed an efficient way to synthesize β-amino aldehydes through the direct, catalytic, and asymmetric anti-Mannich reaction. The reaction was catalyzed by chiral amino acids and amino sulfonamide ligands (**Scheme 8**). MacMillan and co-workers reported an efficient organocatalytic approach to β-amino aldehyde derivatives using the asymmetric conjugate addition of protected hydroxylamines to α,β-unsaturated aldehydes.[34]

3-Aminopropanoic acids bearing a single substituent at C-2 are classified as β^2-amino acids and are found in natural products exhibiting important biological activities.[35] Gellman and co-workers reported the synthesis of β^2-amino acids by the proline-catalyzed diastereoselective aminomethylation of aldehydes (**Scheme 9**).[36] A similar type of methodology has been described by Córdova's group.[37]

Recently, Davis and Song reported the synthesis of syn α-substituted β-amino ketones from chiral sulfinimines and prochiral Weinreb amide enolates, and highlighted their application in the synthesis of chiral amino acids, amino alcohols, ketones, and lactams (**eq 5**).[38]

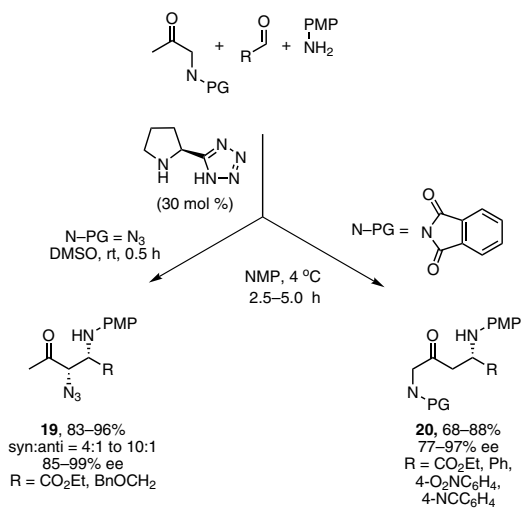
In 2000, Gomtsyan disclosed a direct synthesis of β-amino ketones.[39] Vinylmagnesium bromide was added to amides such as **21**, followed by addition of water to give β-amino ketones **22** in good yields. This procedure worked well for a variety of substituents such as aryl, heteroaryl, and alkyl groups, with the electronic nature of the substituents having little effect on the outcome of the reaction (**eq 6**).

Shibasaki's group reported that imines equipped with a diphenylphosphinoyl (dpp) group on nitrogen can selectively furnish either *anti*- or *syn*-β-amino alcohols.[29c] Similarly, Trost and co-workers have reported the synthesis of *anti*- or *syn*-α-hydroxy-β-amino ketones by a direct, catalytic asymmetric Mannich-type reaction using a dinuclear zinc catalyst, whereby the selectivity was governed by the judicious choice of the protecting group (**Scheme 10**).[40]

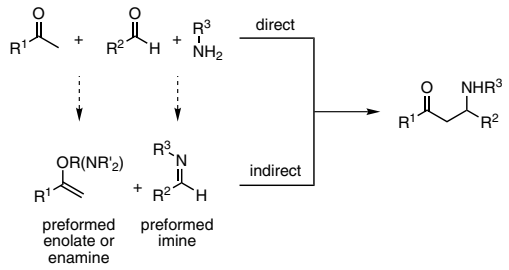
2.3. γ-Amino Aldehydes and Ketones

The synthesis of γ-amino ketones and aldehydes is not as developed as that of the corresponding α- and β-amino compounds. Nevertheless, γ-amino ketones are useful intermediates for the synthesis of five-membered-ring heterocycles.[41] Sato and co-workers[42] reported the synthesis of chiral γ-amino aldehydes and their application in the synthesis of γ-amino acids, pyrrolidinoisoquinolines, and a key intermediate in the synthesis of batzelladine D (**Scheme 11**). Carreira and co-workers developed an elegant approach to β-amino ketones via zinc-mediated reductive scission of 2,3-dihydroisoxazoles.[42b] A "redox-neutral" synthesis of β-amino aldehydes from imines by an alkynylation–hydration sequence was reported by Bolm and co-workers.[42c]

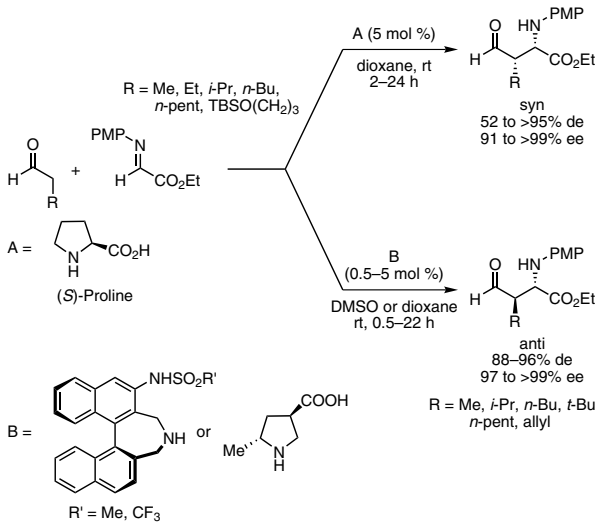
Ma and co-workers[43] outlined the synthesis of γ-amino-β-hydroxy-[44] and γ-amino-α,β-dihydroxy ketones in moderate-



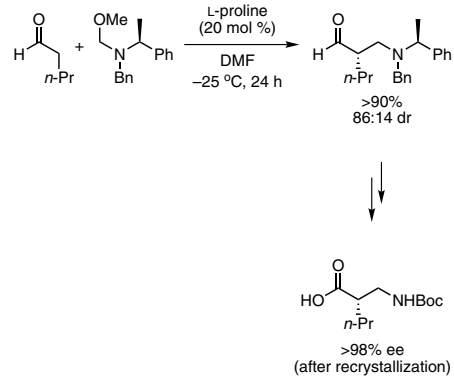
Scheme 6. Amino Ketones by the Organocatalytic Asymmetric Mannich Reaction. *(Ref. 23)*



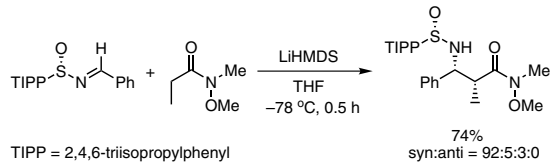
Scheme 7. Mannich-Type Reactions in the Synthesis of β-Amino Carbonyl Compounds. *(Ref. 25)*



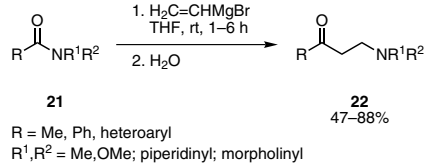
Scheme 8. Preparation of β-Amino Aldehydes by the Catalytic, Asymmetric anti-Mannich Reaction. *(Ref. 30g,32,33)*



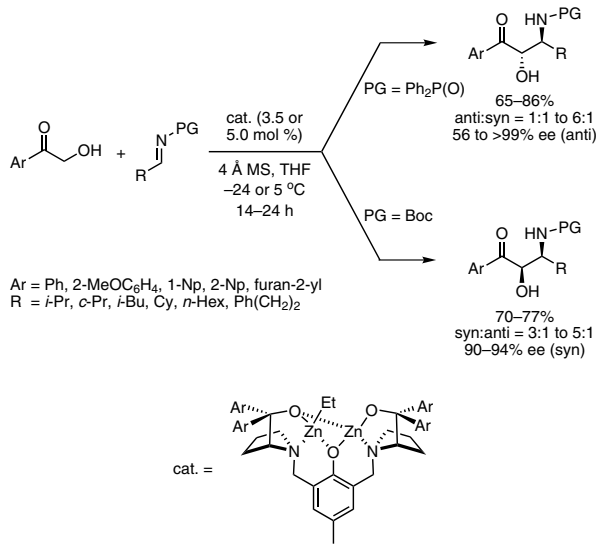
Scheme 9. β²-Amino Acids by the Diastereoselective Aminomethylation of Aldehydes. *(Ref. 36)*



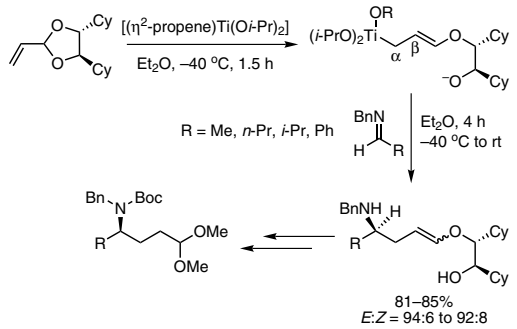
eq 5 *(Ref. 38)*



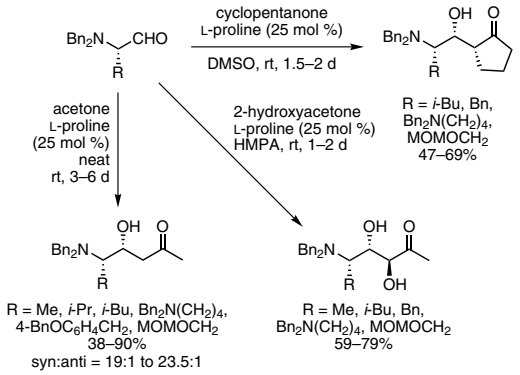
eq 6 *(Ref. 39)*



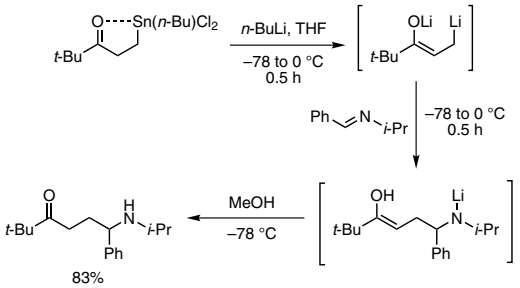
Scheme 10. Trost's Diastereoselective Synthesis of α-Hydroxy-β-amino Ketones. *(Ref. 40)*



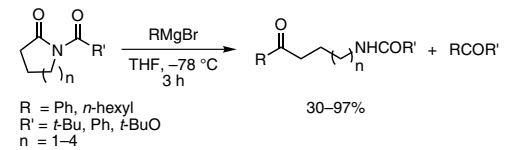
Scheme 11. Sato's Synthesis of Chiral γ-Amino Aldehydes. *(Ref. 42)*



Scheme 12. Ma's Synthesis of γ-Amino Ketones. *(Ref. 43)*



Scheme 13. Ryu's Synthesis of γ-Amino Ketones *(Ref. 45)*



eq 7 *(Ref. 46)*

to-excellent yields and diastereoselectivities. The reaction was performed in the presence of L-proline to catalyze the direct aldol reaction of L-amino acid derived *N,N*-dibenzylamino aldehydes with ketones including acetone, cyclopentanone, and hydroxyacetone (**Scheme 12**).

Ryu[45] and co-workers reported a route to a variety of γ-amino ketones involving the reaction of ketone dilithio α,β-dianions with imines or hydrazones. The dianions were prepared from β-(dichloro(*n*-butyl)stannyl) ketones using excess *n*-BuLi. The enolates added to the imines to selectively form *Z* enolates containing a lithium amide. The *Z* enolates were then transformed into γ-amino ketones and related compounds through reaction with subsequently introduced electrophiles (**Scheme 13**).

2.4. Miscellaneous Amino Aldehydes and Ketones

Savoia and co-workers[46] reported the synthesis of ω-amino ketones[47] from the corresponding Boc-protected cyclic amides. The efficiency of ketone formation decreased with increasing ring size. They also described the use of other protecting groups including pivaloyl, Cbz, and benzoyl. Boc-protected amides were found to be optimal in this chemistry (**eq 7**).

In 1993, Asensio et al.[48] reported that tetrafluoroborate salts of primary, secondary, and tertiary alkylamines are resistant to nitrogen oxidation by methyl(trifluoromethyl)dioxirane (TFDO), which allows for the selective oxidation of aliphatic secondary and tertiary C–H bonds in the alkyl side chain. Thus, when amine **23** was subjected to oxidation by TFDO, the initially formed amino ketone **24** led to cyclic imine **25** as the final product. Alternatively, linear amine **26** furnished ε- and δ-amino ketones **27** and **28** (**Scheme 14**).

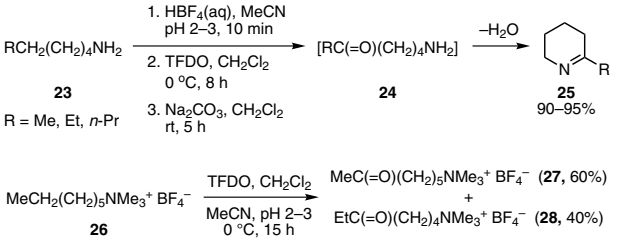
Porantherine, an alkaloid containing an ω-amino ketone subunit, was synthesized by Corey and Balanson.[49] The difference in acid lability between the ketal and acetal functionalities of compound **29** was exploited in performing selective amine-carbonyl condensation reactions. When compound **29** was treated with 10% HCl, acetal cleavage, followed by intramolecular condensation, furnished the porantherine skeleton **30**. Exposure of **30** to more acidic reaction conditions resulted in the cleavage of the ketal group and subsequent intramolecular Mannich reaction to yield **31**. Selective reduction of the ketone functionality using sodium borohydride, followed by dehydration, gave porantherine (**Scheme 15**).

3. Applications of Amino Carbonyl Compounds in Organic Synthesis

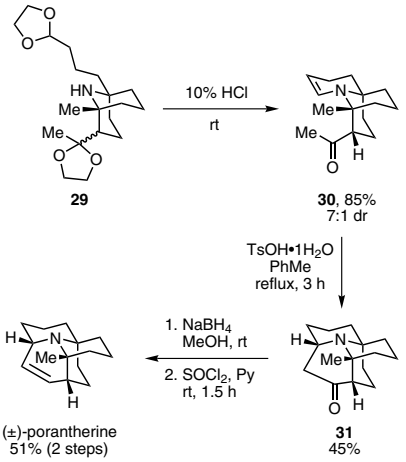
Amino carbonyl compounds are important building blocks in the synthesis of nitrogen-containing natural products, and are widely used in the pharmaceutical industry. Some of the transformations that amino carbonyl compounds undergo include: nucleophilic addition,[50] Wittig reaction,[51] aldol reaction, reductive amination,[52] [3 + 2] annulation,[53] [2 + 2] addition,[54] construction of aromatic and aliphatic cyclic compounds,[55] and formation of cyanohydrin adducts followed by hydrolysis.[50b]

Clive and co-workers synthesized a variety of protected amino aldehydes, and employed them in the Morita–Baylis–Hillman reaction. The resulting adducts were used for the preparation of hexahydroquinolizines, hexahydroindolizines, and related bicyclic structures with nitrogen at the bridgehead position.[56]

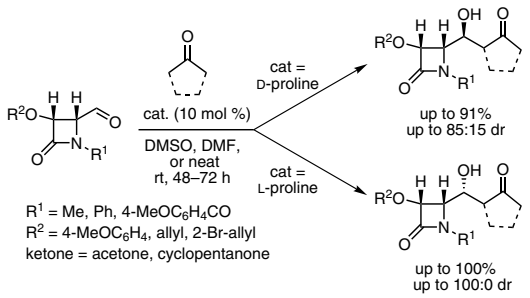
Alcaide et al.[57] recently reported a proline-catalyzed diastereoselective synthesis of γ-amino-β-hydroxy ketones in good yields by the direct aldol reaction between 4-oxoazetidine-2-carbaldehydes and unsubstituted ketones (**Scheme 16**).[57]



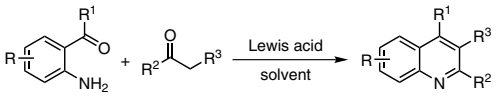
Scheme 14. Miscellaneous Amino Ketones by the TFDO Oxidation of Alkylammonium Tetrafluoroborates. *(Ref. 48)*



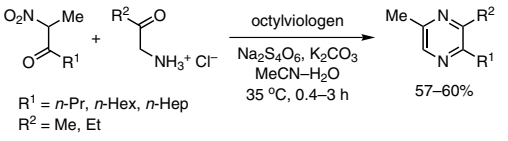
Scheme 15. Corey's Synthesis of (±)-Porantherine, a ω-Amino Ketone Containing Alkaloid. *(Ref. 49)*



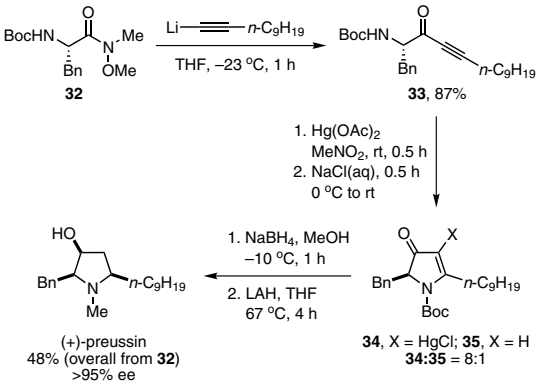
Scheme 16. Application of Amino Aldehydes in the Synthesis of γ-Amino-β-hydroxy Ketones. *(Ref. 57)*



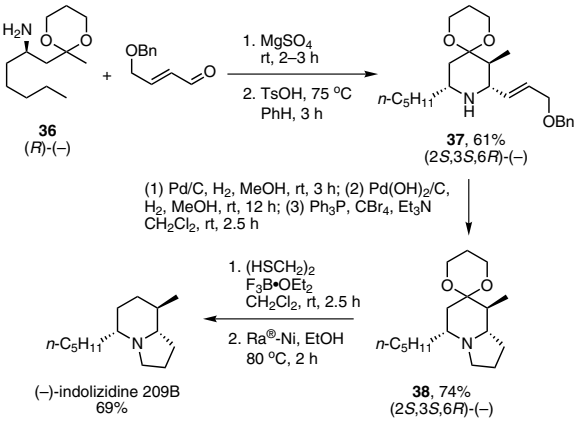
eq 8 *(Ref. 59)*



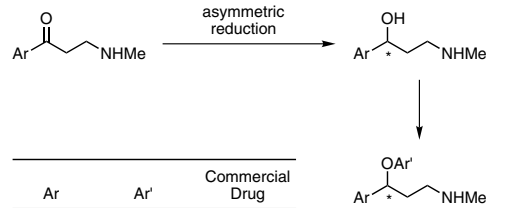
eq 9 *(Ref. 61)*



Scheme 17. Amino Carbonyl Compounds in the Synthesis of Natural Products. *(Ref. 62)*

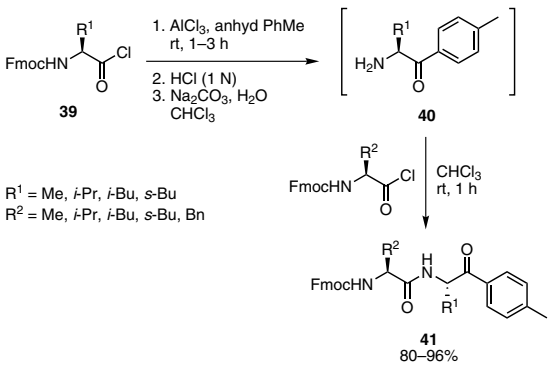


Scheme 18. β-Amino Ketones in the Synthesis of (–)-Indolizidine 209B. *(Ref. 63)*

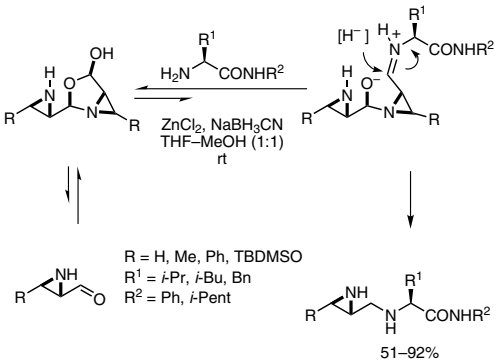


Ar	Ar'	Commercial Drug
Ph	4-$F_3CC_6H_4$	fluoxetine
Ph	2-MeC_6H_4	atomoxetine
Ph	2-$MeOC_6H_4$	nisoxetine
thien-2-yl	1-Np	duloxetine

Scheme 19. Some of the Pharmaceutically Relevant Compounds Synthesized from Amino Ketones. *(Ref. 64)*



Scheme 20. Liguori's Synthesis of Chiral Peptidyl Ketones. *(Ref. 68)*



Scheme 21. Protecting-Group-Free Strategy for Replacing Amide Bonds. *(Ref. 71)*

In general, β-lactams are important pharmacophores for the treatment of diseases caused by bacterial infections.[58]

An important use of amino ketones is in the synthesis of quinolines and their derivatives,[59] which have a wide range of biological activities including antimalarial, anti-inflammatory, antihypertensive, and antibacterial ones. Tyrosine kinase inhibitors and histamine H_3 receptor antagonists were prepared from amino carbonyl compounds.[60] In general, quinolines can be obtained using Skraup, Doebner–Von Miller, and Friedländer methods. Among these procedures, the Friedländer method is best for the synthesis of quinolines involving amino carbonyls as substrates (**eq 8**).

Elmaaty and Castle have reported a facile, regiocontrolled synthesis of trialkyl-substituted pyrazines.[61] α-Nitro ketones were reacted with α-amino ketones in the presence of hydrogen sulfite and octyl viologen as an electron-transfer reagent (**eq 9**). Alkylpyrazines have found utility as flavor components in food, as pheromones, and as versatile synthetic intermediates.

3.1. Selected Examples from Natural Product Synthesis

(+)-Preussin, an antifungal agent, was synthesized in five steps from *t*-Boc-(*S*)-phenylalanine via Weinreb amide **32** (**Scheme 17**).[62] When treated with undecynyllithium (THF, –23 ºC, 1 h), compound **32** furnished ynone **33** in 87% yield. Reaction of **33** with $Hg(OAc)_2$ induced 5-*endo-dig* cyclization to give pyrrolinones **34** and **35** in an 8:1 ratio. The mixture of **34** and **35** reacted directly with $NaBH_4$ in methanol at –10 ºC to give the Boc-protected preussin, which was reduced with LAH to afford preussin.

Davis and Yang reported the synthesis of indolizidine 209B via a β-amino ketone intermediate (**Scheme 18**).[63] The starting amino ketal **36** was obtained from a chiral sulfonamide in three steps and, upon stirring with anhydrous $MgSO_4$ and (*E*)-4-benzyloxy-2-butenal, gave an unstable imine intermediate. The Mannich product **37** was obtained as a single diastereoisomer by heating the intermediate imine in the presence of anhydrous TsOH. Debenzylation of **37** followed by hydrogenation provided bicyclic compound **38**. Treatment of **38** with ethanedithiol in the presence of $F_3B{\bullet}OEt_2$, followed by reduction with Raney®-Nickel led to indolizidine 209B.

3.2. Applications as Building Blocks in the Pharmaceutical Industry

Amino ketones have served as important building blocks in the synthesis of a variety of marketed pharmaceuticals. Through catalytic asymmetric hydrogenation, amino ketones can be converted into enantiomerically pure amino alcohols exhibiting various pharmacological activities. The pharmaceutical industry has implemented this strategy in the enantioselective preparation of several adrenergic receptor agonists including phenylephrine hydrochloride, etilefrine hydrochloride, salbutamol hydrochloride, and adrenaline sulfate.

(–)-Lobeline, an alkaloid isolated from *Lobelia inflate* (Indian tobacco), has been prepared by the asymmetric monoreduction of lobalanine. It is a known nicotinic agonist and has been employed as an antiasthmatic, expectorant, respiratory stimulant,[64] and smoking-cessation aid, with more recent applications in the treatment of psychostimulant abuse.[65]

The amino alcohols derived from the selective reduction of the corresponding amino ketones can also serve as chiral building blocks for the industrial-scale synthesis of other pharmaceutical compounds. In the preparation of the immunoregulating drug levamisole, the intermediate amino alcohol was obtained through selective reduction of the corresponding amino carbonyl.[66]

Fluoxetine (a selective serotonin-reuptake inhibitor), atomoxetine (a selective noradrenaline-reuptake inhibitor), nisoxetine (inhibitor of norepinephrine), and duloxetine hydrochloride (a dual inhibitor of serotonin and noradrenaline reuptake) are important pharmaceuticals, which have been obtained from the corresponding amino ketones by asymmetric reduction (**Scheme 19**).[64] Duloxetine was approved by the U.S. FDA in 2004 for the treatment of major depressive disorder.[67]

3.3. Applications in Biochemistry and Chemical Biology

Di Gioia et al. employed stable and enantiomerically pure Fmoc-protected acid chlorides **39** in a Friedel–Crafts-type reaction to generate chiral α-amino ketones **40**, which reacted in situ with another equivalent of **39** to yield peptidyl ketones **41** (**Scheme 20**).[68] Later, the authors extended this strategy to the preparation of various monopeptidyl ketones and dipeptidyl ketones.

The synthesis of peptidomimetic agents has been an active area of research for a number of years. Protected amino aldehydes have been utilized as aldehyde components in reductive aminations with amino acid containing partners, furnishing CH_2NH_2 linkages in place of selected amide bonds. The resulting reduced amide bond isosteres have received attention due to their propensity to bind at the protease active site.[69] This is possible due to close mimicry of the tetrahedral transition states involved in amide bond hydrolysis. An instructive example in the area of renin inhibition demonstrates that selective replacement of the amide bonds can lead to molecules with improved potency.[70] Although the reductive amination of protected amino aldehydes has been employed in numerous research- and industrial-scale applications, there are significant challenges that face this chemistry. The amino aldehydes as well as their immediate precursors are sensitive to epimerization. In addition, the imine–enamine equilibrium triggered during the reductive amination can lead to epimerization on both the amine and the aldehyde sides of the peptidomimetic fragment. A protecting-group-free strategy for replacing amide bonds with versatile aziridine-containing templates has been developed by Li and Yudin for the synthesis of peptidomimetic molecules (**Scheme 21**).[71] This chemistry is possible due to the dimeric nature of aziridine aldehyde derived intermediates. This feature prevents both overalkylation and epimerization in the course of the reductive amination.

4. Conclusions

Amino carbonyl compounds are versatile synthetic intermediates. Numerous studies have demonstrated their central role in organic synthesis. One can expect that further developments in this field will lead to many more examples where these fascinating molecules partake in strategically significant bond-forming processes.

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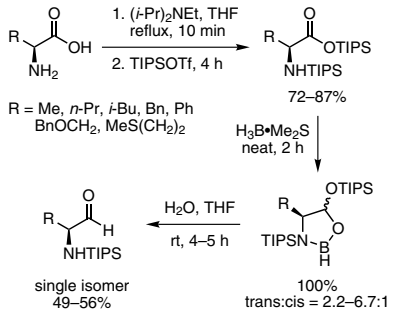
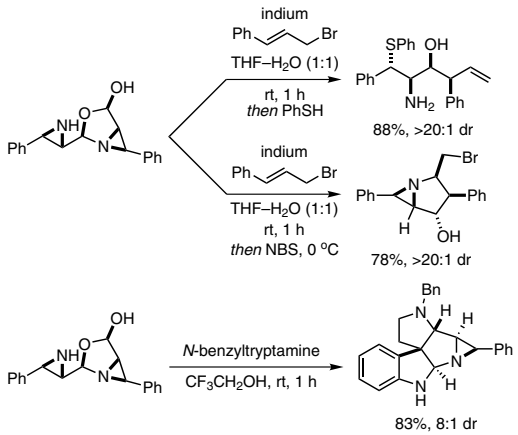
6. Notes Added in Proof

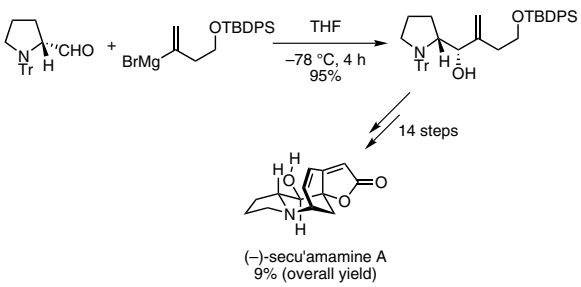
(a) Recently, Soderquist and co-workers have developed a novel borane-based approach to convert α-amino acids into *N*-TIPS-α-amino aldehydes, which were found to be resistant to both degradation and racemization. (Soto-Cairoli, B.; Justo de Pomar, J.; Soderquist, J. A. *Org. Lett.* **2008**, *10*, 333.)



(b) The amphoteric nature of unprotected amino aldehydes has been utilized in the rapid assembly of densely functionalized molecules. Indium-mediated allylation of aziridine aldehydes proceeds with full diastereocontrol, allowing for the one-pot synthesis of either tetrasubstituted pyrrolidines or γ-thio-α-amino alcohols. The nucleophilic nitrogen of the aziridine can also intercept reactive intermediates that are formed in an equilibrium process. Upon reaction of the aziridine aldehyde with *N*-benzyltryptamine, the Pictet–Spengler reaction is interrupted by nucleophilic attack of the aziridine on an iminium intermediate resulting in a complex pentacyclic product. (Hili, R.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4256. Yudin, A. K.; Hili, R. *Chem.—Eur. J.* **2007**, *13*, 6538.)



(c) Weinreb and co-workers recently disclosed their total synthesis of the *Securinega* alkaloid (–)-secu'amamine A. The synthesis began with the Felkin–Anh addition of a vinylmagnesium bromide to *N*-tritylprolinal to produce the desired amino alcohol as a single diastereomer. With this approach, the complex tetracyclic natural product was reached in 15 steps with a 9% overall yield from the α-amino aldehyde. (Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7526. Bejjani, J.; Chemla, F.; Audouin, M. *J. Org. Chem.* **2003**, *68*, 9747.)



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Keywords: amino aldehydes; amino ketones; orthogonal functional groups; aziridine aldehydes.

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Ryan Hili was born in 1983 in Burlington, Canada. He received his H.B.Sc. degree, with a specialist in biological chemistry, in 2005 from the University of Toronto. As an undergraduate student, he worked in the area of nitrene-transfer reactions under the supervision of Professor Andrei. K. Yudin. He remained in the Yudin group to pursue a doctorate degree and is currently in his third year of study. His research is focused on the synthesis and applications of unprotected aziridine aldehydes in organic synthesis.

Andrei K. Yudin obtained his B.Sc. degree at Moscow State University and his Ph.D. degree at the University of Southern California under the direction of Professors G. K. Surya Prakash and George A. Olah. He subsequently took up a postdoctoral position in the laboratory of Professor K. Barry Sharpless at the Scripps Research Institute. In 1998, he started his independent career at the University of Toronto. He received early tenure in 2002, and became Full Professor in 2007. His research interests focus on the development and application of novel synthetic methods that enable the discovery of functionally significant molecules.

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